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SEPTICAEMIA DUE TO MICROCOCCUS TETRAGENUS AS A CAUSE OF PYREXIA AT THE FRONT

By A. H. BIRKS, R. T. THORNLEY, and R. A. FAWCUS

In an admirable work entitled *Les Fièvres paratyphoïdes* Professor Jacques Carles mentions three varieties of blood infection, which produce illnesses clinically indistinguishable from paratyphoid fever.

These three are caused by (1) *M. tetragenus*, (2) Pneumococcus, (3) *Bacillus Coli*.

Of these three types of infection, that by tetragenus is apparently the commonest, followed fairly closely by pneumococcal infections.

There is no doubt of the remarkable frequency of obscure cases of pyrexia at the front at the present moment.

Roughly speaking, they tend to fall into two general types: one resembles paratyphoid fever, and the other, in which the fever is intermittent, is spoken of as 'trench fever'.

The object of this paper is to give a certain number of cases with the bacteriological findings, as an illustration of the fact that often these obscure pyrexias are instances of blood infection by one of the three micro-organisms mentioned.

We believe that a very large proportion of the cases of the illness known as 'trench fever' are instances of one of these infections, and that so also are those frequent cases of continuous pyrexia clinically resembling typhoid in which the presence of none of the typhoid group can be established.

While not at present able to exclude the hypothesis that just as in the later stages of phthisis tetragenus may be isolated in the blood as a secondary infection, so in these cases too it may be a sequela to a primary paratyphoid infection, we regard it as at any rate unproved and as extremely improbable.

Of the three infections, that by tetragenus shows some definite characteristics.

Tetragenus Fever.

The *Micrococcus tetragenus* has hitherto been ignored as a pathogenic organism of importance; in a hundred consecutive cases of obscure pyrexia this organism has been isolated from the blood in pure culture on twenty-five occasions.

Mice when injected with this micrococcus die of septicaemia, and the coccus has been regained from the heart's blood; further, healthy mice, when introduced to the cage of the septicaemic mouse, have contracted the disease and died.

Case I. Pte. M., R.F.A. Admitted 10. 6. 16. ? Erysipelas.

The patient began to feel ill with a 'cold' and some headache which gradually got worse; he also had pains in the stomach (colic) and was very constipated.

Condition on admission. Temperature 101°. Confluent macular eruption over each malar surface, extending down the cheeks and behind the ears; tongue covered with a brown fur; and marked catarrh in the throat, nose, and eyes; some bronchitis. Abdomen full, no spleen to be felt; pain and tenderness over transverse colon.

Course of illness. Continuous pyrexia—complained of pain in legs (marked over the course of the tibia) and back (lumbar).

Steady and gradual improvement; the macular rash remaining for a week, then gradually fading: a patch appearing on the back of the left wrist similar in character; no diarrhoea.

Blood count. R. B. C. 5,870,000, W. B. C. 7,000 per c.mm.

The patient looked anaemic towards the end of his illness. Urine normal.

Inoculation. Typhoid vaccine, two doses within a year.

Bacteriological reports. April 16. *Micrococcus tetragenus* present in blood.

Widal negative to typhoid and to paratyphoid A and B.

Case II. Pte. T. Admitted 31. 4. 16. German measles.

The patient started his illness with a sore throat for about a week; a rash appeared over the face, arms, and chest.

Course of illness. German measles rash disappeared on the third day. The patient had a remittent pyrexia for twelve days, complaining of very little except pains in the knees running down the calf to the ankles. The spleen was found to be palpable. There was no diarrhoea.

Blood count. R. B. C. 5,364,000, W. B. C. 16,000 per c.mm.

Inoculation. Two doses of typhoid vaccine.

Bacteriological reports. 6. 5. 16. *Micrococcus tetragenus* in blood and faeces. 15. 5. 16. *Micrococcus tetragenus* present in blood.

Widal positive $\frac{1}{25}$ to typhoid, negative to paratyphoid A and B.

Case III. Pte. C. Admitted 31. 4. 16. The patient was feeling unwell for four days, and then his headache became worse and he felt generally weak and faint, and on the fifth day of his illness reported sick.

On admission. Temperature 101°. The patient looked ill and flushed, tongue swollen and covered with a white fur. The chest and abdomen had scattered rose spots. The spleen was considerably enlarged.

Course of illness. The patient ran a continuous pyrexia, occasionally remittent, and complained of headache and pains in the back and legs, and became anaemic. The spleen gradually decreased in size. There was no diarrhoea.

Blood count. R. B. C. 3,185,000, W. B. C. 6,200 per c.mm.

Inoculation. Typhoid vaccine, two doses.

Bacteriological reports. 6. 5. 16. *Micrococcus tetragenus* in blood and faeces. 19. 5. 16. *Micrococcus tetragenus* present in blood.

Widal positive $\frac{1}{25}$ to typhoid, negative to paratyphoid A and B.

Case IV. Pte. B. 38½ years.
History of the present disease. The patient felt seedy for a week and went sick on May 25; headache, pains in the legs, and faintness. He was in bed for five days, during which time he was feverish.
Symptoms. Headache; pains in the legs from the knees to the ankles. No sore throat; no diarrhoea.
Physical signs. Well-marked enlargement of the spleen.
Inoculations. Typhoid vaccine, March, 1914, two doses; April, 1916, one double dose.
Bacteriological reports. 8. 6. 15. *Micrococcus tetragenus* present in blood.
Widal negative to typhoid, paratyphoid A, and paratyphoid B.

Case V. Pte. J. Seven months in France. Worked in the wards.
History of the present disease. Pains in the head coming and going; legs and knees a bit stiff for two or three days, but felt better on the evening of the third day. The following morning felt very bad with a headache and pains in the legs.
On admission. Teeth fair; throat slightly injected, no physical signs. Spleen was not palpable. Patient complained of a bad headache and pains in the legs.
Course of illness. Patient ran a remitting pyrexia.
Inoculations. Typhoid vaccine, 1915, two doses; triple vaccine, March 3, 1916.
Bacteriological reports. 8. 6. 16. *Micrococcus tetragenus* present in blood.
Widal positive $\frac{1}{250}$ to typhoid, negative to paratyphoid A and B.
The patient's organisms were clumped by serum of No. II.

Case VI. Pte. F. Seven months in France. Company barber.
The patient came out of hospital five weeks ago and said he had a similar attack then. He never felt well during the five weeks that followed.
History of present disease. On May 6, after lying down in the evening, he got up with a splitting headache, and his legs gave way beneath him so that he could not walk; pains in the legs and generally all over the body; he had a high temperature.
On admission. The patient came in on the eleventh day of the illness; in appearance he looked flushed and had a strained look in the eyes and his face was drawn.
Symptoms. Headache; pains in the legs, back, and neck.
Physical signs. Nil.
Inoculation. Typhoid vaccine, two doses.
Bacteriological reports. *Micrococcus tetragenus* present in the blood.
Widal negative to typhoid, paratyphoid A, and paratyphoid B.
The patient's serum clumped organisms No. II.

Case VII. Corporal H. Eleven months in France.
Previous diseases. Never ill in his life.
History of present illness. The patient felt out of sorts for three days, feeling cold and breaking out into sweats at times.
Symptoms. Headache; pains in legs, knees to the ankles, very marked along the tibia, which was very tender to percussion.
Physical signs. Palpable spleen; rose spots on chest and abdomen.
Inoculation. Typhoid vaccine.
Bacteriological reports. 7. 6. 16. *Micrococcus tetragenus* present in blood.
Widal positive $\frac{1}{250}$ to typhoid, negative to paratyphoid A and B.
The patient's serum clumped the organisms of No. I.

Case VIII. Pte. P. 42. On June 1 the patient collapsed in the trenches, feeling faint and also having a headache, pains in the limbs, knees, and ankles. He ran a remitting pyrexia for sixteen days.

Symptoms. Headache, pains in the limbs and back, cough.

Physical signs. Some bronchitis. The spleen could not be felt.

Inoculations. Typhoid vaccine, March, 1914, two doses; one double dose of triple vaccine in April, 1916.

Bacteriological reports. 10.6.16. *Micrococcus tetragenus* isolated from blood.

Case IX. Pte. L. Patient went sick on June 7 with headache and a sore throat.

On admission. Patient looked very ill—membrane on the throat. Diphtheria bacillus was found on the smear and cultivated.

Course of illness. Patient responded well to antitoxin treatment. The temperature subsided temporarily, but was only normal on two occasions for a period of nineteen days.

Symptoms. Headache; pains in the legs and back, developing while in the hospital; the tibia was extremely tender to the touch.

Physical signs. Rose spots on the chest and abdomen. No spleen could be felt.

Inoculation. Typhoid vaccine, February, 1916.

Bacteriological reports. 13. 6. 16. *Micrococcus tetragenus* isolated from the blood.

Widal positive $\frac{1}{50}$ to typhoid, negative to paratyphoid A and B.

Case X. Pte. O. The patient was admitted on June 3 with a history of a rash on the chest; no rash was however present on admission.

Symptoms. Headache. No abdominal tenderness; no diarrhoea; no pains in the legs.

Physical signs. Nil.

Course of illness. The patient ran a continuous pyrexia.

Inoculation. Typhoid vaccine, March, 1915, two doses.

Bacteriological reports. 7. 6. 16. *Micrococcus tetragenus* present in blood.

Widal positive $\frac{1}{50}$ to typhoid, negative to paratyphoid A and B.

Case XI. Sergt. McQ. The patient was admitted with a rash like German measles; the rash faded on the second day.

Symptoms. No sore throat; some cough. No diarrhoea, constipation, or abdominal tenderness. Headache and pain over the shin-bones marked.

Physical signs. Some bronchitis.

Course of illness. Patient ran a remitting pyrexia.

Inoculation. Typhoid vaccine, March, 1915, two doses.

Bacteriological reports. *Micrococcus tetragenus* isolated from the blood.

Widal positive $\frac{1}{50}$ to typhoid, negative to paratyphoid A and B.

It seems to be the weaker types, or those who have become run down, who fall victims to this form of fever, and in studying the charts and comparing them with the others they show characteristic features. See chart on p. 5.

No. IX after a time developed the remittent character similar to that of trench fever; in many of these cases the pneumococcus has been found, but in this case the blood was unfortunately taken after the temperature had fallen, so the pneumococcus may have been missed though present as a complication.

Clinically the tetragenus cases closely resemble one another. The onset may be sudden or insidious, the former being more common. Headache and pains

in the lumbar region and down the legs from the knees to the ankles occur in nearly every case; tenderness over the tibia is sometimes extreme. Enlargement of the spleen and rose spots occurred in three of our cases. Anaemia is common, and lethargy is the characteristic mental attitude.

Sometimes nothing but slight headache is complained of and the patient runs a low form of pyrexia for a varying period—sometimes for a very long time.
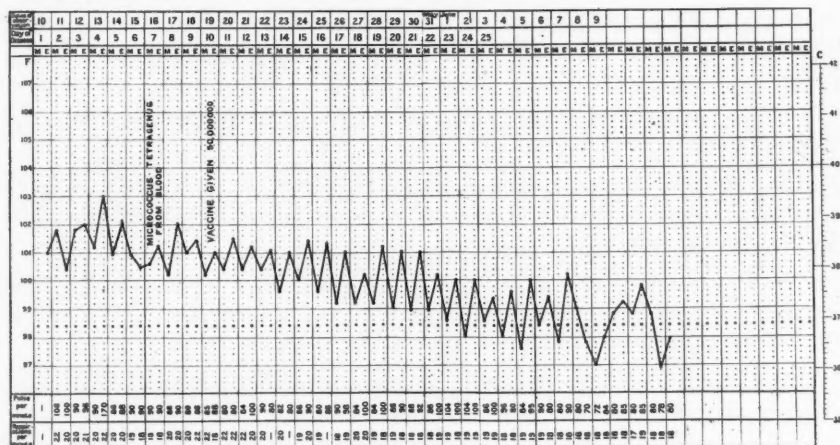
The agglutination of the *Micrococcus tetragenus* by the serum of these patients is a striking feature and clearly indicates that the patients have resisted the infection of the micrococcus.

There is some evidence of the infectious nature of this disease, as orderlies in hospitals are liable to contract it. We have no post-mortem reports of this disease as no fatal case has occurred in our series; but in view at once of its frequency and long duration, it appears to us to be of very great military importance.[1]

Note on 'Coccal' Infections.

Two other well-known cocci—the pneumococcus and the streptococcus—are also common causes of obscure pyrexia at the front. All these three organisms are closely allied in their cultural characteristics, and all produce septicaemia of the same sort of severity, though of different clinical types. The pneumococcus is apparently the cause of the intermittent fever which has been frequently described out here. It also causes another type of illness in which abdominal

[1] The characters of *Micrococcus tetragenus* which we have used for identification are: (1) Profuse growth on ordinary media, sticky and tenacious, without liquefaction; (2) failure to haemolyse blood; (3) strongly Gram-positive rounded coccus, usually in fours with a well-marked capsule; (4) it is very pathogenic to mice and rats, causing fatal septicaemia with some oily pus at the site of injection.

pain, headache, and splenic enlargement, all occurring within the first day or two, are the characteristic symptoms. Thirdly, it may produce a type of fever less distinguishable from tetragenus septicaemia. The streptococcus infection tends to be milder and more chronic, though in its severer forms it is hard to distinguish from the pneumococcal type. In all three fevers splenic enlargement is common. Mixed infections may occur. Probably four out of five cases of obscure pyrexia that we see here are due to one of these three infections. Tetragenus fever is the commonest and most characteristic, and presents the clinical appearance described.

The conclusions we would draw from these and similar cases are the following:

1. The most prevalent type of illness at present at the front in France is a group of continued or intermittent pyrexias of obscure origin.

2. This group tends to divide itself into two general types, of which, apart from bacteriological evidence, one clinically resembles paratyphoid and the other is called trench fever.

3. A large proportion of all these pyrexias are septicaemias.

4. Of these septicaemias the most common is tetragenus fever, which appears to have some characteristic features.

A STUDY OF THE METABOLISM IN A CASE OF AMYOTONIA CONGENITA

By F. POWIS and H. S. RAPER

(The Department of Physiology, University of Leeds)

SINCE Oppenheim in 1901 first described as a clinical entity the disease now known as amyotonia congenita or myotonia congenita, no detailed study of the metabolism in this condition has been made. It seemed, therefore, worth while to make such a study, since the appearances which the condition presents indicate that it may possibly be a nutritional disease of endogenous origin. In favour of this view we might cite the following : (1) the distribution of the amyotonia is always symmetrical; (2) there is a tendency for most of the cases to improve under appropriate general treatment, but the recovery is never complete ; (3) the affection is usually congenital ; (4) the conception that the changes found in the muscles are repressive lesions analogous to those found in the myopathies (Baudouin) is not borne out by the tendency to improvement which the cases show ; (5) the view suggested by Oppenheim, who first described the malady as an arrest of development of the muscle fibres.

Certain features of the metabolism have already been studied by Spriggs (1 in 1907 and Gittings and Pemberton (2) in 1912. Spriggs described observations on a case in which the creatinine excretion was very low compared with a normal child of about the same weight, whereas the uric acid excretion was normal. Gittings and Pemberton confirmed the observation with regard to creatinine, and showed also that there was no departure from normal as regards the calcium retention.

Through the kindness of Dr. Maxwell Telling we have had the opportunity of examining a case diagnosed as amyotonia congenita of medium severity, which was admitted under his care at the Leeds General Infirmary. Although some of the features of this case were not so marked as in certain cases of the disease which have been described previously, the difference was only one of degree.

History and Clinical Features.

L. S., female, aged 4 years, admitted to the Leeds General Infirmary on June 2, 1915, for wasting and general weakness. Patient was born at full term and was fed on cow's milk and added sugar. She did not thrive very well and

never appeared strong like the other children. When a few weeks old she suffered for a short time from attacks of sickness and vomited yellowish matter. She has often been subject to attacks of diarrhoea and vomiting since. When a little over a year old she was still weak and had not begun to walk, though able to crawl a little and progress a few feet whilst holding some support. About this time she attended the Leeds General Infirmary as an out-patient and was treated for rickets. The treatment caused no improvement as far as ability to walk was concerned. When 3 years old she was admitted as an in-patient at the Infirmary, the diagnosis being 'wasting'. At this time she weighed 17½ lb. After a stay of a fortnight she was sent to the Infirmary convalescent hospital, where she remained nearly six months. During this period she gained 10½ lb. in weight but was still unable to walk. During the next six months she gradually fell back to her old condition and was again admitted to the Infirmary as an in-patient in June, 1915. She now weighed 20 lb. It was at this time that she first came under our observation. She is the eighth child and has been the only one to have the symptoms described. Six other children are alive and well ; one of them has had rickets. When the patient was seven months old her father was removed to an asylum for the insane. The family have been in poor circumstances since. The child's appetite has always been poor, and during the last year or two when at home she has been fed chiefly on 'Virol', cocoa, potatoes, and fruit.

On physical examination it was observed that the patient was undersized for her age, and had a starved appearance. The arms and legs looked frail and under-developed. The abdomen was a little full. The face was small but not wasted. She was able to sit up, but could not stand unaided, and could not perform movements with the legs and arms when they were even lightly opposed. The weakness in the legs was more marked than in the arms. The muscles of the limbs were very soft and toneless, and showed the characteristic property associated with the disease of being non-dissociable from the skin and sub-cutaneous tissues. There was no localized wasting of muscular groups and no voluntary paralysis, only weakness. The knee-jerks could not be obtained shortly after admission. There was some flaccidity of the limb joints and marked hyper-extension was produced when the extensor muscles were contracted. The general impression gained, however, was that the degree of looseness of the joints was not so marked as in other cases that have been described. Although the patient was very reserved and quiet, she spoke quite well and normally for her age and station, and did not show any mental defects. The Wassermann reaction was negative.

The case thus appeared to be one of amyotonia congenita, probably in the process of slow improvement, associated with a condition of undernutrition. A specimen of urine passed the day after admission contained large amounts of acetone and acetoacetic acid. On increasing the carbohydrate intake this acidosis promptly disappeared, and two days later at most only a trace of acetone was present. It may be mentioned here that the appetite of the patient during the whole of her stay in hospital was very indifferent. She would take very little bread and butter, milk pudding or porridge, but large amounts of milk or potatoes. With such a whimsical appetite it is easy to imagine that when at home she had been underfed, at least as regards carbohydrate. She would develop an acidosis very readily because of these dietetic peculiarities, and only by the use of syrup or jam with bread was it possible to get her to take enough carbohydrate to keep the tendency to acidosis [1] in abeyance, the minimum amount required being about 60 grm. per day.

The patient was under observation almost continuously from June 2 till November 15, 1915, with the exception of a short period at the end of July when she was discharged by mistake. From November 20 to December 14,

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[1] For the detection of acetone Rothera's test was used.

1915, she was at the convalescent hospital. Metabolic investigations were made in three separate periods: (1) shortly after admission, i.e. June 8 to 12; (2) June 27 to July 2; (3) September 20 to 24. In the first period there was no medication; in the second, cod-liver oil was given; and in the third, dried ox bile. The diet in these periods was free from meat and meat extract, so that observations on the creatine,[2] creatinine, and uric acid excretion could be made. Between the periods meat was allowed. Because of the vagaries of appetite shown by the child, it was never possible to ensure a constant food intake for each day during the metabolic investigations. Although this detracts to some extent from the value of the results it was unavoidable. As regards the main facts ascertained, we do not regard this variation as having much influence.

Evidence of Acholia.

As soon as faeces were kept for examination it was noticed that they were pale in colour, had a foul odour, and possessed the typical glistening appearance of a fatty stool. Determinations of the fat content of the faeces collected during the experimental periods and at other times agreed with this appearance, the amount of fatty substances present in the dried faeces varying from 47 to 60 per cent. Because of the pale colour of the stools a special examination for urobilin and urobilinogen was made in order to determine whether there was any modification in the secretion of bile. One of the daily stools was ground up with 400 c.c. of 0·5 per cent. sulphuric acid and allowed to stand in the light for a week with occasional shaking. On filtering and examining spectro-scopically for the urobilin absorption band it could not be seen. 10 c.c. of the solution were saturated with ammonium sulphate and shaken with a few c.c. of alcohol. The alcoholic layer which separated showed an exceedingly faint urobilin absorption band, but no fluorescence could be obtained on applying the zinc acetate test. It was concluded, therefore, from the fat content of the stools (the fatty substances present were almost entirely made up of soaps and free fatty acids) and the almost complete absence of urobilin and its chromogen, that there was practically no bile entering the intestine. It may be observed here that the child was not jaundiced, and according to the mother's statement she had never shown the slightest trace of jaundice.

The fat utilization determined in the three experimental periods varied from 70 to 79 per cent. Similar figures have been obtained by Schmidt (3) in a careful examination of cases with complete obstruction of the common bile duct. This may be taken as additional evidence, therefore, that a condition of acholia was present. Objection has been taken by von Jaksch, Fleischer (4), and Weintraud (5) to the deduction that acholia is present when pale-coloured fatty stools are passed in which urobilin cannot be detected. It is suggested by these observers that the absence of urobilin may be due to abnormal bacterial action in the intestine, the bile pigments being converted not into urobilin

[2] Since milk contains about 8 mg. creatine and 2 mg. creatinine for 100 c.c., probably a certain amount of the creatine and creatinine in the urine of children taking large amounts of milk is of exogenous origin.

or its chromogen, but into some other substance which does not respond to the tests for these substances. In the present case we have been able to prove decisively that no such abnormal bacterial action was present by administering dried ox bile.[3] When 15 grains per day of this were being given by the mouth it was easily possible to demonstrate the presence of urobilin in the faeces after the treatment with sulphuric acid described above. Both the spectroscopic and zinc acetate tests were strongly positive. The administration of bile was then stopped. Six days later the presence of urobilin could be detected in the faeces, but the amount was markedly smaller than in the period when the bile was being given. Eleven days later only faint traces of urobilin could be detected as originally, i.e. the spectroscopic test was just positive, but the zinc acetate test negative. From August 21 to September 11, 1 grm. daily of crude ox bile salts was administered with the idea of stimulating bile secretion if possible and increasing fat absorption, but no evidence of bile secretion was obtained either by the presence of urobilin in the faeces or improved fat absorption.

We are led to the conclusion, therefore, that for some reason at present obscure practically no bile secretion was taking place in this patient, indicating, therefore, a condition of hepatic insufficiency. The figures obtained during the three periods for the fat utilization and the distribution of fatty substances in the faeces are summarized in Table I. The numbers represent average daily values for the periods.[4]

TABLE I.

			Fatty Acids in Faeces.				
Period.	Medica-ment per day.	Fatty acids from food. (Liebermann.)	As neutral fat.	As free fatty acid.	As soap.	Total fatty acids. (Liebermann.)	Percentage utiliza-tion.
		grm.	grm.	grm.	grm.	grm.	
I.	Nothing	40·6	0·67	5·02 (32)	4·06 (14·5)	10·4	75
II.	1·16 grm. cod-liver oil	33·4 (including cod-liver oil)	0·22	4·16 (18)	2·01 (12)	7·0	79
III.	1 grm. dried ox bile	28·4 (44·3)	0·38	5·88 (23)	1·80 (13)	8·6	70

The figures in round brackets are the iodine values.

General Data for the Experimental Periods.

The first and third periods lasted four days, the second five days, always starting and finishing at 8 a.m. In each period the food consisted of milk,

bread and butter, potatoes, and, during the first period, also milk pudding, this being refused during the succeeding periods. The milk formed the chief source of nutriment. The average amount of protein, fat, and carbohydrate consumed on each day of the three periods, together with their approximate caloric values, are given in Table I A.

TABLE I A.

Period.	Protein. grm. per day.	Fat. grm. per day.	Carbohydrate. grm. per day.	Total cals.	Cals. per kilo body weight.
First	39·7	47·0	97	990	105
Second	29·6	36·6	80	780	80
Third	27·3	31·7	60	650	65

The method of sampling the food for analysis is given in the appendix.

In calculating the above, the protein has been taken as 6·25 times the total nitrogen, the fat as 1·11 times the amount of fatty acids, and the carbohydrate as the difference between the total weight of dry food and the sum of the weights of protein and fat, allowing 6 per cent. of the air-dry food to be moisture, as found when a sample for the first period was dried in a desiccator. During the second and third periods the child did not eat so well as before and after; exactly why we cannot say, but apparently there was some objection to the special counterpoised plate on which the food was weighed. We intended to avoid using this during the third period, but after the first day the nurse was changed, and it was again used by mistake.

Throughout the first period acetone and aceto-acetic acid could not be detected in the urine, but small amounts were present on the third, fourth, and fifth days of the second period, and second, third, and fourth days of the third period.

In accordance with the larger food intake, acetone was very rarely present in the urine at other times than during the metabolism periods.

Judged by the behaviour towards Fehling's solution, glucose was present in amounts slightly larger than normal. On one occasion the rotation was determined and corresponded to the presence of 0·19 per cent. of glucose in the urine passed, or a total for the day of 0·7 grm.

The appearance of the faeces has already been mentioned. During the three metabolism periods they were usually slightly alkaline or amphoteric to litmus, being slightly acid on only one occasion.

Mineral Metabolism.

An investigation of the mineral metabolism was carried out in the experimental periods in order to determine (1) the degree to which the alkali and alkaline earth bases together with phosphoric acid were being retained; (2) the influence of cod-liver oil (period 2), and bile (period 3), on the mineral balances; (3) whether the ratios between the amounts of the several bases were

such as would be obtained in a normal child of the same age or weight ; and (4) whether the medication adopted caused any notable variations in the mineral retentions. The third question cannot be answered at present because of lack of data, and it will not be possible to give this comparison until the figures for a number of normal children have been obtained ; these we hope to get in the course of time, but the work is time-absorbing and somewhat laborious, so this point must be left for discussion till later.

The figures given in Tables II, III, and IV represent average daily values for the several periods. In an appendix a summary of the analytical procedures is given.

TABLE II.

First experimental period.   8 a.m. June 8 to 8 a.m. June 12.
No medicine given.

Constituent.	Food.	Urine.	Faeces.	Total output.	Balance.	% of amount in faeces which dissolved in alcohol.
	grm.	grm.	grm.	grm.	grm.	
P_2O_5	2·488	1·101	0·854	1·955	0·53	1
CaO	1·772	0·009	1·317	1·326	0·44	13
MgO	0·241	0·064	0·153	0·217	0·024	18
K_2O	2·435	1·590	0·507	2·097	0·34	96
Na_2O	0·963	0·697	0·064	0·761	0·20	82

TABLE III.

Second experimental period.   June 27 to July 2.
Medicament 1·16 grm. cod-liver oil per day.

Constituent.	Food.	Urine.	Faeces.	Total output.	Balance.	% of amount in faeces which dissolved in alcohol.
	grm.	grm.	grm.	grm.	grm.	
P_2O_5	1·844	0·626	0·453	1·079	0·765	2
CaO	1·345	0·008	0·579	0·587	0·76	4·5
MgO	0·191	0·034	0·062	0·096	0·095	1
K_2O	1·682	0·775	0·314	1·089	0·59	95
Na_2O	0·640	0·437	0·064	0·501	0·14	88

TABLE IV.

Third experimental period.   Sept. 20 to Sept. 24.
Medicament 15 grains dried ox bile daily.

Constituent.	Food.	Urine.	Faeces.	Total output.	Balance.	% of amount in faeces which dissolved in alcohol.
	grm.	grm.	grm.	grm.	grm.	
P_2O_5	1·629	0·589	0·857	1·446	0·183	1
CaO	1·285	0·034	0·906	0·940	0·345	1
MgO	0·175	0·042	0·127	0·169	0·006	2
K_2O	1·47	0·768	0·508	1·276	0·19	88
Na_2O	0·612	0·354	0·129	0·483	0·13	85

The figure for Na_2O in the third period includes that present in the dried bile, viz. 0·057 grm., the amount of K_2O being negligible compared with that in the food.

The collected results in Tables II, III, and IV show that the mineral balances in all three periods were positive, and most markedly so in the second period, when cod-liver oil was being given. The effect is most marked on the phosphorus, calcium, and potassium retention, the sodium being but little affected. This effect of cod-liver oil on the calcium retention has been noted also in cases of rickets, and its curative action in this disease is referred to this property. We are not aware of any previous demonstration of its effect on the potassium retention by comparing the same person with and without cod-liver oil, but Meyer (21) found that two children with rickets who were taking cod-liver oil showed a high calcium but low potassium retention. The effect of bile administration is not the same as that of cod-liver oil, the total mineral retention in this period being considerably smaller.

The striking feature of all the periods, and especially the first two, is the large amount of potassium retained relatively to calcium. Owing to the lack of complete data concerning the relation of potassium to calcium retained in normal children, the matter is difficult to discuss. Certain general considerations, however, may be referred to. The greater part of the calcium in the body is in the bony tissues, and the greater part of the potassium in the soft tissues. The relative amounts of the two bases retained, therefore, in the growing animal, would be dependent on the rate at which these two types of tissue were being laid down. We are not aware that any data have been obtained showing what variations in the degree of retention of these two bases occur as an animal grows, but it is very important that they should be known. Assuming for the present that the bones and muscles (which represent the greater part of the soft tissues) grow at about the same rate, then we may take the amounts of calcium and potassium in the ash of a young animal as giving approximately the ratio in which these two bases should be retained. In the ash of young animals Bunge (6) found for one part by weight of CaO the following amounts of K_2O: dog, a few hours old, 0·39; four days old, 0·24: cat (young), 0·30: rabbit (fourteen days), 0·31. He quotes figures for a newborn child which give a ratio of K_2O to CaO of 0·27, whereas Hugounenq (23) found a ratio of 0·153. In rats of the same litter we have found a ratio of 0·69 when three days old, and of 0·39 when twenty-three days old, the ratio of the amounts retained during the twenty days being 0·34 of K_2O to 1 of CaO.

The ratio obtained in the present case was 0·78 to 1 in the first two periods and 0·55 to 1 in the third. Since no abnormal condition of the bones has been noted in amyotonia congenita, and since the absolute calcium retention in the first period when no medication was adopted is of the same order as that found in normal children, the calcium retention may be considered to be normal. This view is also supported by the findings of Gittings and Pemberton (2) in the case they investigated. We are led to the conclusion, therefore, because of the high ratio of the potassium to the calcium just mentioned, that potassium is being retained in this condition in amounts above the normal. The destination of this potassium is uncertain, since we have no comparative analyses

of the soft tissues, and especially the muscles, in children suffering from amyotonia and normal children. It seems, therefore, that some such determination should be made when an opportunity offers. The theory, however, is attractive, that the structural abnormalities in the muscles which have been demonstrated by Baudouin (7) and Collier and Holmes (8) in this disease may be associated with a relative increase in their potassium content. This can only be determined by future investigation.

Nitrogenous Metabolism.

The partition of the nitrogenous substances in the urine was determined daily in the three periods. Since accurate separation into twenty-four hour periods was not possible in a child 4 years of age, slight variations from day to day were noticed. The figures given in Table V represent the average per day during each period.

The nitrogen balance in all the periods was positive, the average daily retention being 1·23 grm. in the first, 1·17 grm. in the second, and 0·31 grm. in the third period.

TABLE V.

	Period I.		Period II.		Period III.	
	Absolute amount.	% of total N.	Absolute amount.	% of total N.	Absolute amount.	% of total N.
	grm.		grm.		grm.	
Total nitrogen	4·51	—	3·25	—	3·44	—
Ammonia	0·38	6·95	0·325	8·2	0·32	7·6
Urea	8·24	85·4	5·64	81·0	6·06	82·3
Uric acid	0·154	1·14	0·150	1·54	0·168	1·63
Creatinine	0·069	0·57	0·066	0·75	0·067	0·72
Creatine (reckoned as creatinine)	0·126	1·04	0·105	1·20	0·124	1·34
		95·1		92·7		93·6

The average amount of nitrogen per day in the faeces was: first period, 0·61 grm.; second period, 0·305 grm.; and third period, 0·63 grm.

The striking features demonstrated by the figures in Table V are the low amounts of creatinine excreted and the relatively large amount of creatine present daily. Almost two-thirds of the 'total creatinine' is present as creatine. The observations published by Spriggs (1) and by Gittings and Pemberton (2) on two other cases of amyotonia congenita do not include the figures for creatine in the urine, but in both cases the creatinine excretion was much below the normal. The figures from these cases, together with those found in the present case and some from normal children, are given for comparison in Table VI.

TABLE VI.

Case.	Age.	Weight.	Daily creatinine excretion (mg.).	Mg. creatinine per kg.
	yrs.	kg.		
Amyotonia—				
(Spriggs)	$4\frac{1}{4}$	13	60	5
(Gittings and Pemberton)	$1\frac{3}{4}$	11	17	1·7
(Powis and Raper)	4	9·7	67	6·9
Normal children—				
F. P. R.	3	14	231	16·5
(Another period)			239	17·1
G. B. L.	$2\frac{1}{2}$	14	192	14

Gittings and Pemberton also investigated two children as normal and found 7 and 8 mg. creatinine per kg., but since in both cases the nitrogen balance during the period was negative, it appears doubtful whether they can be considered normal. They, as well as Spriggs, also used the old Folin method of estimation, which is not very accurate for urine of low creatinine concentration.

The creatine excretion observed in the present case, compared with that found in the two normal boys, is given in Table VII.

TABLE VII.

Case.	Age.	Weight.	Daily creatine (mg.).	Mg. creatine per kg.	% of 'total creatinine' as creatine.
	yrs.	kg.			
Amyotonia	4	9·7	118	12·1	64
Normal—					
(1) F. P. R.	3	14	25	1·8	9·6
(Another period)			59	4·2	20
(2) G. B. L.	$2\frac{1}{2}$	14	81	5·8	30

Other periods with F. P. R. gave 18·3 and 17·6 per cent. of the 'total creatinine' as creatine.

Folin and Denis (22) also give figures for the twenty-four hours' creatinine and creatine excretion of three normal children on a meat-free diet, though the two where the collection was continued more than one day were 11 and 8 years old respectively. For the second and third days the mean amounts of creatinine per kilo body weight were 11·8 and 12·9 mg., the creatine being 3·0 and 4·0 mg., and the percentage of 'total creatinine' as creatine 21 and 23 respectively.

The percentage of 'total creatinine' present as creatine and the creatine excreted per kg. of body weight are much higher in the amyotonia case than in the normal children. The interpretation of these variations, however, is difficult at present because of our ignorance of the reason why creatine is normally found in the urine of children and not in that of adults. Since the creatinine excretion of an individual is now generally held to be a function of the amount of muscle he possesses, the low creatinine excretion in the present case may reasonably be explained by the small bulk of the muscles.

It has been suggested above that in the present case there was evidence of a diminution in the functional activity of the liver. Mellanby (9) has

produced evidence that the liver plays some part in creatine metabolism, especially as regards its production and utilization by muscle. The evidence obtained in the present case gives some support to this view, for maldevelopment of the muscles and hepatic insufficiency are associated. It seems possible that the utilization of creatine is dependent on certain processes carried out by the liver. Another view, advocated by Cathcart (10), which is not essentially different from Mellanby's, is that utilization (resynthesis) of creatine is a function of the muscles and is dependent on the adequate maintenance of the carbohydrate metabolism ; if this fails then creatine is excreted because it cannot be resynthesized. The case under discussion would support this view in so far as the diminished functional activity of the muscles is concerned, but evidence has not been found that the creatine output was influenced by the amount of carbohydrate in the diet. This may be partly due to the fact that milk formed the chief food. The largest amount consumed on any day of the three metabolism periods was 1,325 c.c., whereas the smallest amount was 545 c.c., i.e. a difference of about 800 c.c., which would therefore correspond to about 64 mg. of exogenous creatine. It is therefore possible that any increased endogenous creatine when the food intake was small may have been practically balanced by the diminished exogenous. That the child was not able to utilize creatine given by the mouth was shown by administering on one day 0·206 grm. of creatine, when practically the whole of it was excreted in the ensuing forty-eight hours.

General Progress of the Case.

For the first few weeks the patient made very little improvement, as judged by increase in weight, increase in strength of the muscles, and observation of the knee-jerks. The strength of the muscles was tested roughly by causing the patient to lie flat on her back and measuring the height to which she could raise either foot from the bed. Three months after admission she could only raise the left foot four inches and the right foot three inches. The knee-jerks were present in both legs, but more easily elicited in the left, though the response was very poor. About this time the administration of bile salts was begun, and four weeks later a marked difference in the strength of the legs was noticed, the child being now able to raise either leg to a position almost at right angles to the trunk. The nurse in attendance also noticed that the child was more active in bed and could get up from the recumbent to a sitting posture more easily. She could not stand without assistance, however, and could not walk. The administration of bile salts or dried bile was continued, except for two periods of a fortnight each, until November 20, when the child was sent to the convalescent hospital. Her weight at this time was only $2\frac{1}{4}$ lb. greater than when admitted on June 2, but she was noticeably stronger. Through an oversight the administration of bile salt was stopped when transference to the convalescent hospital took place. She remained there three weeks

and was discharged on December 13, her weight having increased by a further 3 lb. She was still unable to walk when discharged.

During the whole period of observation she had no attacks of diarrhoea and vomiting such as the mother had described; in fact, the bowels were generally constipated. There was also no fever.

Summary and Conclusions.

Since the data presented above are obtained from a study of only one case of amyotonia congenita, and that associated also with some nutritional disturbance, it is not intended to enter into a deep discussion of the results. It is only by an investigation on similar lines of other cases that the constant metabolic disturbances of the disease can be determined. The cases are by no means common, so the authors feel justified in publishing this account of a single case in order that those having access to others may be able to confirm or disprove the constancy of the abnormal features noted.

The chief findings may be summarized as follows:

(1) A diminution of hepatic functional activity as manifested by the presence of acholia. Whether this is an accidental association or is of importance in the pathology of the disease can only be determined by a study of other cases.[5]

(2) A normal calcium retention associated with a relatively high potassium retention.

(3) A low creatinine excretion as established by previous observers, and accompanying this a relatively high creatine excretion. Until more is known about the formation of creatine, its rôle in the body and the reasons for its appearance normally in the urine of children, this high creatine excretion cannot be explained.

(4) Treatment of the case with bile salts or dried ox bile produced some improvement, as manifested by an increase in strength of the muscles, and a change towards the normal in the ratio of the potassium to the calcium retention, the normal values, owing to a lack of other data, being deduced from the ash analyses of young animals.

Appendix.

Sampling food and collecting excreta. Samples of the food were taken each day in the same proportion as actually consumed, and the mixture evaporated to dryness on a water-bath. The residue in the dish was allowed to stand twenty-four hours so as to attain approximate moisture equilibrium

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[5] We have been able to find in the description of autopsies performed in cases of amyotonia only one reference to the liver. Griffith and Spiller (*Amer. Journ. Med. Sci.*, cxlii. 165) described the liver cells as much vacuolated (fatty infiltration) and the lumen of the large bile ducts as filled with granular material.

with the atmosphere, weighed, and the food ground and kept in stopped bottles. The faeces were transferred quantitatively to a weighed dish, evaporated, and ground like the food. A small water enema was given just after the start and at the end of each period, so that the faeces should represent the period as nearly as possible. Each sample of urine for the twenty-four hours was poured as soon as passed into a bottle containing a little toluene and 100 c.c. of water, the latter being to cool the first samples more quickly. All the estimations of the nitrogenous compounds in the urine were made within ten hours of the end of each twenty-four hour period, and an aliquot portion also measured out for the determination of the mineral matter for the whole period.

Determination of mineral constituents. In the case of food or faeces the removal of the organic matter was carried out by dry ashing as recommended by Aron (11). In the case of urine, a quarter of that from each day was taken and the mixture evaporated to syrupy consistency; the oxidation of the organic matter was then accomplished with the aid of nitric acid. In determining the percentage of the mineral constituents in the faeces which was soluble in alcohol, a suitable amount was extracted until nothing further dissolved, by allowing the hot alcohol to fall from a condenser into the Soxhlet thimble and from this into the flask from which the alcohol evaporated, the boiling being stopped occasionally so as to allow the thimble to drain. The alcoholic extract was quantitatively transferred to a dish, the alcohol removed on a steam bath, and the residue dry ashed like the food. The residue in the thimble was allowed to dry, then removed as completely as possible, and dry ashed.

After removal of the whole of the organic matter and any silica, the hydrochloric acid solution of the residue was made up to a definite volume.

Potassium and sodium were estimated in one part by isolating the mixed chlorides by the method recommended by Aron (12), except that lime-water was substituted for baryta, and after the first precipitation of the excess of calcium ammonium oxalate was used instead of the carbonate. Aron states that the calcium carbonate precipitate is difficult to filter, but this becomes quite easy if it is heated for a time on the water-bath; should any calcium remain in solution it is subsequently precipitated as oxalate. Especially with the urine, where nitric acid had been used, care was taken to ensure that only chlorides were present. The potassium was then estimated by the method of Davis (13), with the precautions suggested by Thin and Cumming (14).

For calcium and magnesium McCrudden's (15) method was used, except that no sodium phosphate was added for the precipitation of the magnesium; in all cases except that of the alcoholic extract of the faeces the solution itself contained quite sufficient phosphate. Consequently, by adding magnesia mixture to the filtrate from the magnesium determination, or to an aliquot part of it, a second precipitate of magnesium ammonium phosphate was obtained, and the sum of the two gives the amount of phosphate present. A freshly prepared Gooch crucible was used for each precipitate. In the case of the alcoholic extract of faeces the filtrate from either the calcium or first magnesium precipi-

tate can be divided in two, so as to enable both magnesium and phosphorus to be estimated. A few of the duplicate estimations of phosphorus were made by Neumann's method using the factor 1·243, which had been found suitable with a standard solution under the same conditions. These agreed well with those by the above method.

Nitrogen compounds. For these the following methods were used : total nitrogen, Kjeldahl ; ammonia and urea, Van Slyke and Cullen (16); uric acid, Folin and Macallum (17), but with the standard solution of Folin and Denis (18); creatinine and creatine, Folin (19), suitable precautions being taken when acetone was present. With urine containing very little creatinine, one or two precautions are necessary to ensure accuracy, but it is intended to refer to these in a paper dealing specially with creatinuria in children.

All the determinations were made in duplicate except those for the mineral constituents of the faeces, where the sum of the part soluble and insoluble in alcohol, compared with that in the whole, gives a sufficient check. For the duplicate estimations of urea the simpler method of Marshall (20) was used, and for ammonia the formaldehyde method, the results by this being about 10 per cent. greater than by the other method.

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RECORDS OF SPEECH IN GENERAL PARALYSIS

By E. W. SCRIPTURE

With Plate 1

In general outlines the speech disturbance in general paralysis has been described as showing in its initial stages the phenomena of slowness, monotony, hesitation, tremor, syllable-stuttering, paraphasia, &c. Later, the speech is said to become blurred and lisping. Still later, there is aphasia and asymbolia. It is said that the peculiarities are a mixture of cortical and bulbar symptoms, with predominance of the cortical ones at first and the bulbar ones later. Attempts have been made to systematize and explain the phenomena of elision, reduplication, transposition, &c.

All this is extremely vague. If a patient over forty years of age persistently stumbles over ' Peter Piper's peppers ' and similar phrases, the symptom tells heavily in favour of general paralysis. Yet I have known an epileptic boy with no possibility of general paralysis to do exactly the same thing. The so-called ' syllable stuttering ' — which bears not the slightest resemblance to real stuttering—appears just as markedly in some cases of motor aphasia.

It is necessary to find some method of studying the speech of paretics that will give very definite and incontrovertible data concerning the speech disturbance. This method should also be made to yield the information before the ear can detect any change and even before the other symptoms are sufficiently marked to afford a correct diagnosis.

An appropriate method of studying speech has been developed by phoneticians, and for many years has been used to register the minute variations due to nationality, dialect, and individual peculiarities. These variations are all so small that they lie within the limits of normality. The method has the advantage of recording the speech just as it comes from the mouth of the speaker ; there can be no errors of observation and no discussion or disagreement concerning how the person spoke. Again, the records can be studied at leisure with microscope and measuring apparatus ; the data are preserved and always at hand for verification. Finally, the results are obtained automatically by measurement and computation ; the conclusions are not opinions of any observer but are the incontrovertible records themselves. When such a method is applied to abnormal cases, the diagnosis is settled the moment the patient has

made a record. What the diagnosis must be would then be automatically revealed by the study of the record.

Some eight years ago I began this line of work. In the beginning I found that the first problem was to adapt the method to clinical and bedside observations. The cumbersome recording apparatus had to be reduced to portability; the entire outfit can now be packed into a hand-bag. The next problem was to develop methods of measurement, computation, and presentation that would yield the results within a reasonable time. A complete analysis of a single sentence can now be made with about five hours of work; with an assistant this can be reduced to two hours. Such a complete analysis is often unnecessary. Some diseases have been found to give records so characteristic that a glance at them is sufficient to yield a positive or a negative answer.

About twenty cases of general paralysis have been studied. They range from those where no speech defect could be detected by the ear to those far advanced toward dementia. For the present occasion I shall consider only the milder cases where the speech disturbance was not very marked. The advanced cases furnish illustrations of almost the entire psychology of the disease, and the account must be reserved for another occasion.

The recording apparatus is shown in Plate 1, Fig. 1. The revolving cylinder is covered with smoked paper. The recorder is a development of the phonautograph idea (Scott, Marey, Rousselot).[1] When a person speaks into the metal mouthpiece, the vibrations and the puffs of air travel to an oiled-silk membrane whose movements are recorded by a lever on the blackened surface of the revolving cylinder.

A normal record of 'hippopotamus' is given in Fig. 2. There is a slight rise in the line as the initial 'h' is produced. This is followed by the vibrations of 'i'. These are cut short where the line descends as the lips close for the occlusion of 'pp'. The line rises as they open for the explosion of this sound. The next 'p' has a somewhat stronger explosion. For 't' the occlusion is shorter and the explosion weaker, as is usual in this word. The occlusion for 'm' shows faint vibrations. The raised line for 's' registers the current of air from the mouth.

A normal record of 'Peter Piper's peppers' is shown in Fig. 3. The 'p's' are registered as straight horizontal lines (occlusions) ending in sharp upward jerks (explosions). The record of 't' is similar, but shorter and weaker. The small waves register the vowels. The 's' is a raised line.

Records of a case of general paralysis with apparently no speech defect are reproduced in Figs. 4 and 5. The patient, V., 40 years old, fell while driving a carriage six years before presenting himself; he was unconscious for about an hour. Six months later he began to have 'spells' at intervals of about every three months until six months before. The last attack was the most severe.

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[1] For the methods of recording speech, see Rousselot, *Principes de la phonétique expérimentale*, Paris, 1897; Scripture, *Elements of Experimental Phonetics*, Yale University Press, 1902.

h i pp o p o t a m u s

FIG. 2. *Record of 'hippopotamus' by a Normal Voice.* The small rise of the line for the air issuing from the mouth during 'h' is followed by the waves of the vowel 'i'. These are cut short as the lips close to form the 'pp' (there is, of course, really only one 'p' here, not two as the spelling might indicate). During the 'occlusion' the lips remain closed and the line is a straight one. The sudden rise is due to the puff of air—the 'explosion'—of 'p' as the lips open. The second 'p' sound, the 't', and the 'm' all show occlusions with explosions. The 's' shows a long raised line that registers the continuous current of air from the mouth. Between these consonants the vowels appear as series of vibrations.

P e t er P i p er's p e pp er s
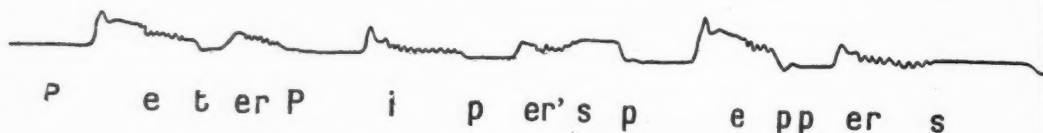
FIG. 3. *Record of 'Peter Piper's peppers' by a Normal Voice.* The occlusions and explosions for 'p' and 't' and the 's' are registered as in Fig. 2.
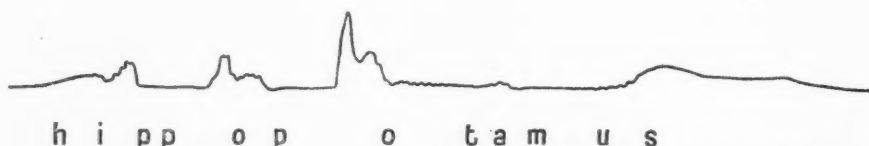
h i pp o p o t a m u s

FIG. 4. *Record of 'hippopotamus' by a Paretic Voice.* The explosions of 'p' and 't' vary from nothing to very strong; the occlusions vary greatly in length. These are examples of asaphia (cortical ataxia).

P e · t e r P i p er' s p · e pp

er s
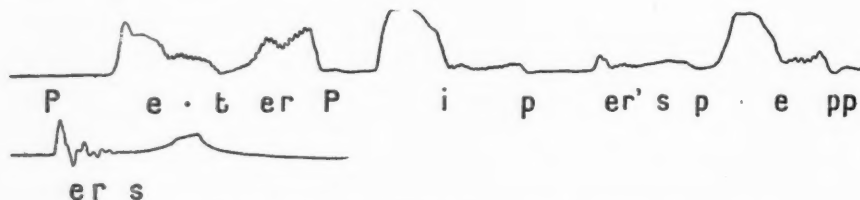
FIG. 5. *Record of 'Peter Piper's peppers' by a Paretic Voice.* The explosions vary enormously, the occlusions almost as much. These are examples of asaphia (cortical ataxia).

150

100

50

Pe ter Pi per's pe ppers
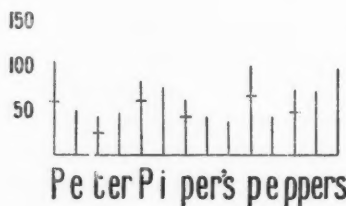
FIG. 6. *Duration Chart to Fig. 3.* The durations are given in thousandths of a second. The line under the cross-line represents the duration of the occlusion, and the line above, the duration of the explosion.

The spells were said to be epileptic in character.   His face had a dull expression. The left pupil was larger than the right and did not react to light; the right pupil reacted promptly.   There was horizontal nystagmus.   Some weakness of the left facial nerve was noticed.   The knee-jerks were normal.   His memory was poor; he was sluggish, disinclined to work, and very irritable.   He had a tendency to answer very briefly.   With the ear it was impossible to detect any abnormality in his speech.
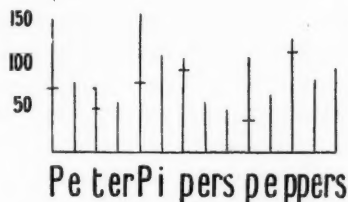
FIG. 7.   *Duration Chart to Fig.* 5.   The durations are given in thousandths of a second. The line under the cross-line represents the duration of the occlusion, and the line above, the duration of the explosion.   The durations vary from the type.

The patient was examined by a number of neurologists who all pronounced him a well-marked case of general paralysis without speech defect.   This patient's record of 'hippopotamus' (Fig. 4) shows at a glance a marked difference in the heights of the explosions for the two examples of 'p', whereas no great difference appears in the normal record (Fig. 2).   The 't' has almost no explosion.

Since the recording cylinder is revolving at a constant speed, distances along the horizontal line will represent the durations of the sounds.   In the normal record the durations for the occlusion of 'p', 't', and 'm' are not very different.   In the paretic record the first 'p' with a weak explosion has a longer duration than the second 'p' with a strong explosion; the 't' is almost lacking and the 'm' is much prolonged.

The abnormalities in force and duration are strikingly shown in the record of 'Peter Piper's peppers' (Fig. 5).   Two examples of 'p' have violent explosions, two have moderately strong ones, and one has a very faint one.   The duration of the occlusion in 'p' varies from rather long in the last 'p' to very short in the 'p' before it.   There is no relation between duration of occlusion and strength of explosion; a violent explosion may go with a short occlusion or a long one.

The durations in the normal and the paretic records of 'Peter Piper's peppers' are shown in Figs. 6 and 7.   The irregularities in the paretic record are evident.

Although the sounds shown in this record are not correctly made, they do not show the bizarre irregularities of movements affected by ataxia.   Each 'p' in the record is a fairly good 'p' and is not misunderstood or mistaken for some other letter.   The 'p' with excessive explosion would be quite normal in Irish;

the 'p' with no explosion is the proper one in French; that with excessive length of occlusion is the regular one in the dialect of Zürich. Although they are all forms of the sound 'p', and although each one of them would be considered as a type if the others were like it, yet the patient varies through all possible types, with no system or irregularity. The condition is that of an uncertainty in the idea of type rather than in movement. The result is a lack of precision in speech. For this phenomenon the term 'asaphia' (Greek, σαφῶς, precise) is better than the misleading one of 'cortical ataxia'.

Although the irregularities of asaphia appear so markedly in the records, it must be remembered that they were too small to be detected by the ear. Here we have a firm basis for a diagnosis at a time when the ear reveals nothing.

No matter whether other symptoms are present or not, if the speech record is positive for asaphia we must assert the presence of general paralysis or some other condition producing this symptom. Asaphia never appears in neurasthenia, psychasthenia, mania, or melancholia. With a positive record these diseases can be excluded at once. The limitation from arterio-sclerosis and diffuse syphilis of the brain is not yet clear.

If the record is negative for asaphia, the result tells heavily against general paralysis. All the records that I have made of this disease have shown this symptom.

A more advanced case may now be considered. The patient, K., 52 years old, was pronounced by several neurologists to be a marked case of general paralysis with speech defect.

His pupils were equal but small; they reacted to accommodation but not to light. There was considerable tremor of the facial muscles, especially around the mouth. The knee-jerks were normal. His demeanour was marked by loquacity, euphoria, some traces of grandiose ideas and a considerable defect of memory. His writing showed irregularity, but no errors.

The record of 'hippopotamus' (Fig. 8) shows a sudden intake of breath followed by a rise of the line for 'h'; there is some irregularity in the breath pressure as shown by the wavering of the line. The syllable 'po' was repeated three times; at first normally and then with steadily shortened occlusions and weakened explosions for the 'p', and with shortened duration and weakened vibrations for the 'o'. The first 'p' has a duration of 0·105 sec. and a height of 8 mm.; for the second 'p' the figures are 0·091 sec. and 6 mm.; for the third 'p' they are 0·077 sec. and 2 mm.; for the first 'o' they are 0·133 sec. and 0·5 mm.; for the second 'o', 0·119 sec. and 0·4 mm.; for the third 'o', 0·077 sec. and 2 mm.

After the last repetition of 'po' there follows an interval of 0·273 sec. There is next a strong rising of the line with strong vibrations; the rise of the line is the result of the air blown out for 'h'. The strong vibrations indicate the vibrations of the vocal cords. This is a sonant 'h'; although the sonant 'h' is usual between two vowels, it is not found as an initial sound in English. The vibrations that follow for the vowel 'i' are rather weak. The bad adjustment

of the breath and laryngeal tone is evident. The following 'p' has a very long occlusion and a weak explosion. The rest of the word is spoken correctly, but the explosion and the vowels are very weak, except at the end of the last vowel. The 's' is well marked.

The enunciation of the word may be indicated approximately as follows :

<p style="text-align:center">hippo po po ɣ hippopotamus</p>

The repetition of the second syllable is like that of a person who is trying to cling to something in his mind by repeating it until he can get back the next thing he wants to say. Apparently the patient hung on, gently repeating the syllable 'po' until his thought had faded away. He then started freshly from the beginning of the word and got it right in the main.
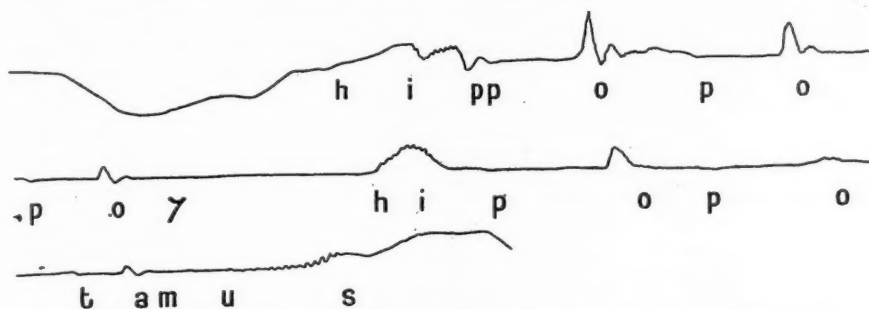
FIG. 8. *Record of 'hippopotamus' by a Paretic Voice.* The variations in explosions and occlusions (asaphia) are very marked. The repetition of the syllable 'po' (perseveration) was due to an attempt to hold the syllable in mind till the whole word could be brought up. This indicates a defect of recollection.

In attempting to say the familiar phrase, the patient said 'Peter's Piter's pepepepers' (Fig. 9). The initial 'p' of each of these three words has an exceptionally strong explosion. The other occlusives, namely 't' in the first two words and 'p' in the last word, have exceptionally weak explosions. He apparently pronounced the word in three measures with a strong beat at the beginning of each measure. The 's' sound is erroneously added to the first word, corresponding to the similar sound which comes correctly at the end of the other words. The last word shows a very strong initial 'p' with the regular vowel waves. The second syllable is an occlusion without an explosion, followed by four vowel waves that make up about one-fourth of the usual short vowel. Then follows a long occlusion for a 'p' with an explosion and a regular set of vowel waves. The last 'p' is rather weak.

The asaphia in this case was evidently much more severe. In addition there are examples of transposition, reduplication, and 'syllable stuttering'. These furnish excellent examples of apraxia, amnesia, and alabia in the following manner.

To attain a certain result, the person must determine what part of the body he must move, which line of movement is to be followed, how the parts are to be

moved in combination and succession, and how the end is to be reached. If he wants to get a glass of water from the table to his lips, he must know that he is to use his hand and arm, that the hand must reach the glass, clasp it, and raise it to the mouth. The action of the brain whereby the selection is governed is called 'praxia'; a disturbance of it is called 'apraxia'.

Ataxia produces irregular movements. Asaphia produces unprecise ones. Apraxia often produces wrong movements or some that do not correspond to the intended purpose, although they may be correct for another purpose. The apraxic may put a wrong sound in a word, but, if no ataxia or asaphia is present, the sound itself will be correct.
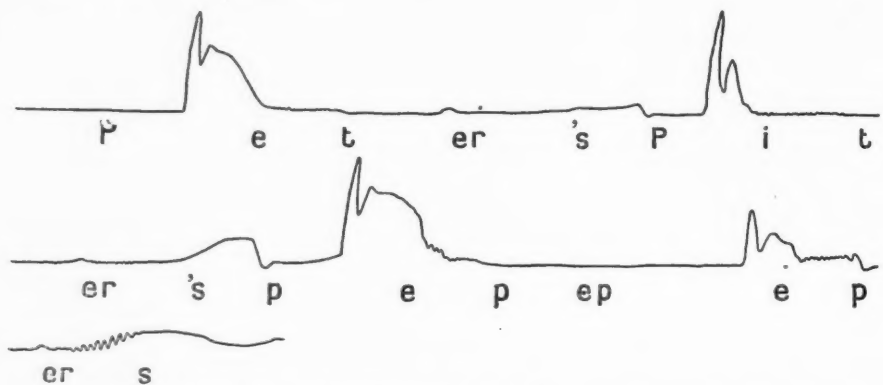
FIG. 9. *Record of 'Peter Piper's peppers' by a Paretic Voice.* The irregularities in explosions and occlusions are very marked. The insertion of the 's' in 'Peter's', the use of 't' in 'Piter's' (assimilation), and the reduplication in 'pepepeppers' are examples of apraxia.

Apraxia may be divided first into three forms: motor, transmissional, and ideational. In Liepmann's chief case, when the patient was told to put his right hand to his nose he said 'Yes', and executed wide circling movements in the air; when told to put his left forefinger on his nose he did so at once. It was evident that he knew visually (and could describe) the course his right forefinger must take, that he could describe the action of his elbow, &c., but that he did not know how to govern his right arm. Such a condition is termed 'motor apraxia'.

In saying 'hippopotamus' the patient may get the word as a whole fairly correct while making the sounds imperfect in a way not found in ataxia or asaphia; the larynx does not start and stop at the proper moments; the lips are closed too soon or too late; the tongue is moved in an incorrect way. The sounds are thus irregular and distorted. The result is the blurred speech found in later stages of general paralysis.

In 'transmission apraxia' the patient may wish to make a complex movement, such as speaking a word, but, although the separate sounds may be produced properly, they do not come at the right places. He may say 'Peter's Piper's peppers' (Fig. 9), putting a correctly formed 's' at three places instead of two. He knows he has spoken it wrongly and knows just what sounds

should be in the phrase, but any attempt at speaking it produces transpositions and similar errors because his ideas go wrong in being transmitted into action; the correct formation of the single sounds shows that the motor praxic centre is intact.

In 'ideational apraxia' the person may have a general idea of the action he wants to perform but his notions of its parts and details is vague or impaired. A patient observed by Liepmann received a cigar and a match-box. He opened the box, stuck the cigar in and tried to shut the box—evidently carrying out the action of cutting the end of the cigar instead of striking a match. Then he rubbed the cigar on the side of the box, as if lighting a match. A similar error in speech was that of the paretic who spoke of 'sweating fish' instead of 'swimming fish'.

A perseveration like 'hippopopo' in Fig. 8 might be classed as an example of ideational apraxia. It is, however, evidently due to the inability to hold a complex word firmly in mind; the patient hangs on to the syllable 'po' by repeating it until the rest of the word comes up. This indicates a deeper mental defect of the nature of a weakness of memory grasp (alabia).

Since speech is the most delicate, sensitive, and complete method of expressing mental activity, it is natural to expect to find in the speech of paretics the best method of studying the mental disturbance in this disease. The speech records show traces of practically the entire mental derangement of the paretic. It is quite unjustifiable to lump them all together as 'ideational apraxia'. If we attempt to analyse them and assign them to their causes, we get a picture of the mental disturbance in general paralysis. Such an attempt must be made in order to gain a complete understanding of paretic speech. This involves, however, complete analysis of the mental disturbance in this disease, and would lead too far for the present occasion.

The marked distinction from fatigue-neurasthenia lies in the records of enunciation. The neurasthenic may alter the speed of his speech but the individual sounds will keep their relations of duration. Likewise he may speak with a faint voice, but his record will not show any fine irregularities of intensity. In short, asaphia is shown in the record of the general paralytic as an early symptom, whereas it never occurs in neurasthenia. This affords a possibility of avoiding the most frequent mistake in diagnosis of early cases.

DESCRIPTION OF FIGURE.

PLATE 1, FIG. 1. *Recording apparatus.* The cylinder is covered with paper and blackened in a flame. It is made to revolve at high speed. The speech waves pass down the tube and move the membrane of the recorder. These movements are enlarged and registered on the cylinder by a straw lever.
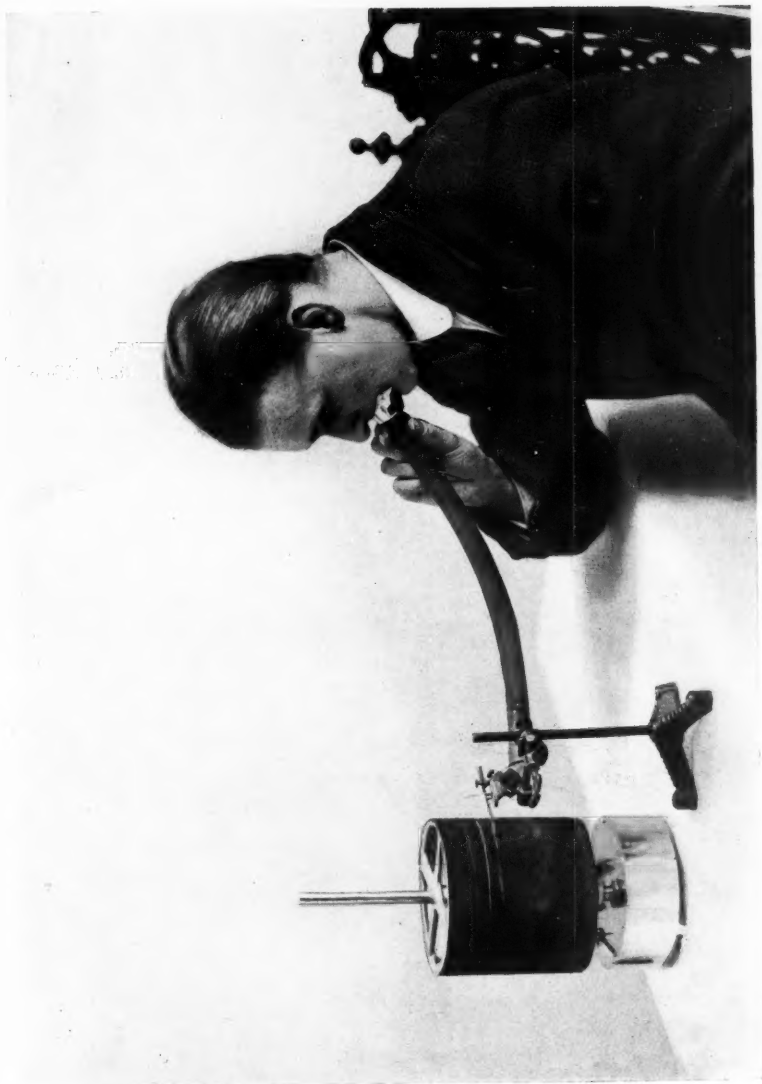
FIG. 1

THE RETINITIS OF ARTERIO-SCLEROSIS, AND ITS RELATION TO RENAL RETINITIS AND TO CEREBRAL VASCULAR DISEASE

By R. FOSTER MOORE

(From Moorfields Eye Hospital and the Ophthalmic Department,
St. Bartholomew's Hospital)

With Plates 2–9

I. The Ophthalmoscopic Evidences of Retinal Arterio-sclerosis.

THE following investigations have been carried out with three main objects in view :

(1) To define, as accurately as possible, those changes in the retina and its vessels which are indicative of arterio-sclerosis; to apportion to these changes their relative importance; and to follow their development and course over considerable periods of time.

(2) I hope to establish that a condition of retinitis may be engrafted on retinal arterio-sclerosis; that this retinitis has distinctive characters; and that in its course and prognostic significance it differs markedly from renal retinitis and calls for separate recognition.

(3) I have considered in detail the extent to which disease of the retinal vessels is an indication of similar disease of the cerebral vessels.

Source of Material.

I have drawn exclusively upon two sources for the clinical material, viz. St. Bartholomew's Hospital and Moorfields Eye Hospital. I have to express my best thanks to all the Medical Staff at St. Bartholomew's. They have given me every facility to examine the patients under their care in the wards, and during the last three years I have fully availed myself of the opportunities thus afforded. I am also indebted to Prof. Andrewes for permission to acquire in the post-mortem room a number of eyes which I had examined ophthalmoscopically from time to time during life. My best thanks are due to my colleagues at Moorfields; not only have they given me a free hand to choose suitable cases

from their clinics, but have often been at considerable pains to remember and supply my wants, and so have rendered these investigations possible.

It will be noticed that whilst all the patients who will come under consideration have been the subjects of general arterio-sclerosis, they divide themselves naturally into two groups corresponding with the source from which they are derived. Thus, one group have presented themselves at an ophthalmic hospital, i. e. the vascular disease has especially involved the *retina*, and has produced such impairment of sight as to induce them to seek advice on this account. In them the evidence of cerebral vascular disease, when present, has usually only been obtained on inquiry. The second group, on the other hand, consists entirely of patients who have been suffering from the results of *cerebral* vascular disease for which they have been admitted to a general hospital. In them the ocular vascular disease has for the most part given rise to no symptom and has only been discovered on examination.

Methods of Examination.

All the examinations at Moorfields have been carried out by myself. Many of the patients have been examined over long periods at intervals of four or six weeks, and the minute changes in the retina followed by means of accurate outline drawings. The visual fields have been charted in a number of cases on several occasions each. In most cases the systolic blood pressure has been estimated at each visit, and the figures given in the tables represent the average for all the examinations; Martin's modification of the Riva-Rocci sphygmo-manometer has been used. The urine has always been examined as to its specific gravity and the presence of albumin or sugar, on one or several occasions.

The ophthalmoscopic examination of the patients at St. Bartholomew's has in every case been carried out by myself, but for all the other particulars I have been dependent upon the physician under whose care the patient has been placed. The clinical diagnosis in every case is that of the physician, except when, the patient having died, an autopsy has been obtained; I have then made use of the actual post-mortem findings.

The patients upon the examination of whom the bulk of this work has been carried out consist of 66 seen at Moorfields and comprised in Tables A and B, and of 44 seen at St. Bartholomew's comprised in Table D. An endeavour has been made to keep those seen at Moorfields under observation up to the present time, or till the time of their death. All those seen at St. Bartholomew's were already the subject of cerebral vascular disease, and have, therefore, not been further traced.

The difficulty of keeping in touch with patients, owing to their migratory habits, is notorious, and more especially is this true in London. Having this in mind, I have almost from the first observed the precaution of taking, in addition to the patient's address, the address of their medical adviser, and, what I have

found more valuable in this class of case, the address of one or more of their close relatives. By this means I have succeeded in tracing 59 out of 66 patients, and of the 7 untraced, the address of the patient only was taken in 5 cases.

The Ophthalmoscopic Signs of Retinal Arterio-sclerosis.

To Marcus Gunn (5) the credit is due for having first accurately defined those characters of the retinal vessels which are indicative of retinal arterio-sclerosis, and for showing how close is their relation to cerebral vascular disease.

The changes described by him may be shortly summarized as follows:

(1) Irregularity of lumen of the retinal arteries.

(2) Tortuosity of the arteries.

(3) An exceptionally narrow and bright central light streak which may show a series of brighter points at intervals.

These changes are of chief importance when they involve the tertiary and secondary branches of the retinal artery.

(4) Loss of translucency of the arterial walls.

(5) Obstruction of the blood-flow in the veins where they are crossed by arteries.

(6) Oedema of the retina.

The extended experience of physicians and ophthalmic surgeons has served to confirm the accuracy and importance of Gunn's work: it is therefore proposed to consider only those particulars in which the present observations tend to amplify, or in one or two instances to modify, the observations of Gunn. The headings and the order of the headings used by Gunn will be preserved here; I wish, however, to emphasize that the sign included under the fifth head is considerably the most valuable and important single sign of severe arterio-sclerosis.

1. *Irregularity of lumen of the arteries.* A high degree of arterio-sclerosis may occur without any irregularity of the arterial lumina being present; when, however, this irregularity is present, it is an indication of severe disease and a high or very high blood pressure. The narrowing of the artery develops somewhat gradually as the vessel is traced along, until the lumen may be reduced to one-half or less of its original diameter; it then dilates again to its former size, and this process may be repeated several times in the same vessel as it is traced towards the periphery (Figs. 1, 2, 4).

Less often the reduction of the lumen is more sharply limited, so as to take on the nature of a localized constriction. This may be seen in all grades of the retinal arteries, and is always associated with an abnormally bright reflex which is usually dotted (*vide infra*).

It seems probable, as suggested by Coats (1), that more or less localized areas of endothelial proliferation are responsible for the appearances. He has pointed out that subendothelial proliferation is the common disease of the *central* retinal arteries, whereas in *its branches* in the retina mesarteritis is more common,

and this is in accord with the comparative rarity with which irregularity of lumen is seen in the retinal arteries.

The blood supply to the tissues of the retina must be somewhat precarious where narrowing of the arteries is marked, and I have given reasons for thinking (2) that the pressure in such a vessel may be less than the normal, although the systolic pressure in the brachial artery is 250 mm. Hg. or more. In extreme cases defects of the visual fields may be found, but a high grade of narrowing may occur without any discoverable defect. A marked constriction of the artery may remain quite unchanged, both as regards itself and the vessel beyond, for several years.

Fig. 1 represents an outline drawing of the retinal arteries of the left eye of Case 22, made on Sept. 13, 1913.

She was seen on March 4, 1916, when the condition was quite unaltered; there were no haemorrhages nor other change present in the retina.

It has been suggested that localized spasm of the arterial wall may be responsible for the appearance. General spasm of the retinal, as of other arteries, does of course occur; it is seen in its most marked form in quinine amaurosis, but whether localized almost ring-like constrictions can take place I do not know; I have not seen them, and it seems unlikely that a highly diseased vessel should be capable of severe spasm. It is clear that in the case referred to above the appearance was due to organic change in the arterial wall.

I have seen a marked degree of irregularity develop in eight months. The patient, a soldier, who had previously had no illness, developed retinitis in association with 'trench nephritis' in August, 1915. The retinitis has now (April 16, 1916) subsided to a remarkable degree, and irregularity of lumen of the arteries is quite marked: his blood pressure is 200 mm. Hg.

In some cases of post-neuritic optic atrophy, and in some other cases, narrowing or apparent narrowing of the arteries *on the disk* is seen, but when these vessels are traced outwards they attain a full normal diameter. I suspect that this appearance, limited as it is to the disk, has an optical basis.

2. *Tortuosity of arteries.* An increase in bulk of the tissues which form the middle coat of an artery, whether by hypertrophy, or as a result of fibrosis or hyaline degeneration, must of necessity increase the length of the vessel at the same time that the thickness of the wall is increased, and increased tortuosity necessarily results. This, however, is seldom extreme in degree, and is one of the less valuable of the signs of arterio-sclerosis, and especially so since variations in tortuosity are so wide under physiological conditions. The small vessels in the macular region occasionally show extreme tortuosity, a condition to which the term 'corkscrew arteries' is applied. Whilst this is a valuable sign when present, it is so seldom seen that it must be considered as one of the less important signs. The explanation of the development of tortuosity in the arteries which is given by Gunn is to the effect that, owing to loss of elasticity of the vessel wall and to narrowing of the lumen, the blood current is impeded, and the tortuosity is to be regarded as the result of the *vis a tergo* acting upon a tube which has lost its carrying power.

3. *The central light reflex.* This is one of the most important of the signs of arterio-sclerosis, and is, I believe, of universal occurrence in this disease. The appearances consist, as described by Gunn, of an unusual brightness of the central light streak and of the artery as a whole, and, in cases which are severe, the central streak, besides being bright, is slightly irregular, with brighter dots at short intervals.

The value of these appearances is detracted from to some extent by the fact that we are dealing with an exaggeration of normal appearances, which themselves vary somewhat widely; consequently it may be impossible to say, in an individual case, whether the degree of brightness of the reflex is within normal limits, and there is a tendency amongst medical clerks and house physicians, whose experience of these signs is of necessity somewhat limited, to diagnose arterio-sclerosis first, and afterwards to discover bright retinal arteries. It is therefore proper to urge that too much emphasis should not be placed on the existence of bright arteries in the absence of any other sign of retinal arterio-sclerosis; that this sign should be looked for in the branches of the artery of the second and third dimension, and that the significance of the bright reflex is greatly enhanced if it is irregular or dotted in appearance. The appearance is due, as stated by Coats, to fibrosis of the middle coat of the vessel, for the artery seen in section in Fig. 15 had during life an exceedingly bright and burnished appearance; it was as bright as any artery I have ever seen.

4. *Loss of translucency of the arterial wall.* When a vein crosses deep to an artery it can in some healthy subjects be seen dimly through the latter; when, however, the arterial walls become thickened, not only is the vein hidden where it lies deep to the artery, but for some distance on each side of the actual crossing it is invisible owing to the thickening of the arterial walls, and the course of the vein appears actually to be broken.

This sign is considered further under the next heading.

5. *The phenomena to be seen at arterio-venous crossings.* I believe the signs to be considered under this heading are the following:

(1) They are never seen apart from arterio-sclerosis.

(2) They are always present in sclerosis of any considerable degree.

(3) The variations in their degree are so easily made out that they form a really reliable means of judging the extent to which the sclerosis has developed.

Gunn laid considerable stress upon the evidence of obstruction to the flow in the veins where they are crossed by sclerosed arteries, but laid no stress upon the displacement of the line of the vein at such crossings. He dismisses it by saying that sometimes the vein may be slightly pushed aside. I believe this displacement of the line of the vein is the most striking and important single sign of severe retinal arterio-sclerosis.

The phenomena will be considered under two heads: (A) Evidence of obstruction to the flow in the veins; (B) Displacement of the line of the vein.

A. *Evidence of obstruction to the flow in the veins.*   The retinal veins are capable of distension to a degree much in excess of that normally found in health, as is seen in cases of leukaemia, &c. : if, therefore, the lumen of the vein is severely obstructed at the arterial crossing a marked degree of distension of the vessel peripheral to the crossing might be expected, a condition to which the term ' banking ' is often applied.   I do not doubt that the flow in the vein is obstructed, but I am convinced that any considerable or very obvious degree of banking is but rarely seen, and if one had to rely upon this evidence alone, one would be compelled to state that there was but slight evidence of obstruction to the venous flow.

The two following observations, however, are of interest in this connexion : (1) It occasionally happens that a vein is crossed twice by the same artery within a short distance and that no tributary is received by this short length of vein ; in this case the trapped portion of the vein may be much reduced in calibre, whilst beyond the respective points of crossing its lumen is of full size. (2) It is much more usual in the retina for the veins to cross deep to the arteries, but a vein may occasionally be found which *crosses over* a highly sclerosed artery, in which case it is in view throughout its course and the actual narrowing of its lumen can be seen (Plate 7).

B. *Displacement of the line of the vein.*   Normally where an artery crosses a vein, at whatever angle, the line of the vein at, and on each side of, the crossing is not even slightly diverted.   In the earliest stage of sclerosis of the artery the line of the vein will remain unaltered, but the vessel will be hidden under the artery and for a narrow margin on each side of the arterial wall, as has already been explained.   As, however, the thickening of the arterial wall develops, the line of the vein comes to be diverted, and the more marked the sclerosis the greater is the displacement of the line of the vein.

In a case of marked arterio-sclerosis in which a vein and artery converge to cross very obliquely it will be found that as the vein approaches the artery, instead of continuing its direct course, it is first diverted slightly so as to lie alongside the artery ; it then passes under the artery, and, having reached the other side, again lies alongside the artery for a very short course before continuing in its former line.

The line of the artery is not altered.

In a case of very severe sclerosis the vein, though meeting the artery at an angle, say, of 15° and leaving it at a similar angle, passes under the artery at right angles to its (the artery's) course (Fig. 14).   The effect attained is that the vein, instead of taking a long course under the artery, as would be the case in a very oblique crossing, traverses from one side to the other by the shortest possible route.

The same phenomenon may be seen, and *in no less degree,* where a vein crosses *over* an artery.   This, however, occurs much less often.   Plate 5 represents a drawing made from Case 33 on April 28, 1914, and Fig. 14 is an accurate representation of the same crossing as seen on March 10, 1916 ; that is

to say, no change had taken place in its appearance in the course of two years, and it is evident that this condition must have been present for some considerable time, probably several years previous to April, 1914. Thus, whilst there would appear to be considerable obstruction to the vein lumen, it had not, in the course of two years for certain, produced haemorrhages or any other change in the territory drained by this vessel.

In conditions such as myelogenic leukaemia, where great distension of the veins may be present, they may be severely cut into where they are crossed by healthy arteries. I do not, however, remember to have noticed lateral displacement of the vein in such a case.

In a case of renal retinitis (3) I have watched the displacement become less marked coincidently with the reduction in the size of the vessels as the retinitis subsided.

6. *Oedema of the retina.* Gunn speaks of cases in which there is an absence of the full red reflex rendering examination without a mydriatic very difficult, and attributes this to the presence of general oedema of the retina. I have used a mydriatic as a routine in all my cases, and consequently have not met with this difficulty. I have found no reason to look upon general oedema of the retina as a sign of arterio-sclerosis.

Other Changes in the Arteries.

General reduction in size. It is difficult to say whether the arteries in an individual case are reduced in size, where direct comparison with the normal is not possible, and where the normal itself varies. I believe, however, that this should be considered as one of the signs of arterio-sclerosis.

Conversion into fibrous threads. In some cases so extreme is the sclerosis of the arteries that a fine axial stream of blood is seen, bordered on each side by a broad, sharp-cut opaque white band representing the greatly thickened arterial wall. Ultimately the lumen may completely disappear and the former vessel come to be represented by a white thread. I have watched this process occur gradually in a number of cases (Case 53, Fig. 9). In such cases discoverable visual defects are always present.

Retinal Haemorrhages.

Retinal haemorrhages are exceedingly common with retinal arterio-sclerosis, and are properly looked upon as merely an incident in this disease; I have, therefore, not mentioned their existence or otherwise in Tables A and B. In some cases, however, an increase in their number occurs coincidently with the onset of other serious symptoms, or as a precursor to such. I believe the occurrence

of these haemorrhages is immediately due to an impairment in nutrition of the vessel wall and to changes in the blood.

That disease of the vessels in a very small localized area of the retina may be at times responsible for the haemorrhages is exemplified in Case 35, Table A. On July 8, 1913, he had three groups of small dotted retinal haemorrhages, the rest of the retinae being quite free; and on April 1, 1916, $2\frac{3}{4}$ years afterwards, these same small areas of the retinae were the site of haemorrhages which were now somewhat larger, and the rest of the retinae were still perfectly clear and free of haemorrhages (Fig. 6, No. 5). I believe, for the following reasons, that the haemorrhages are not directly related to the hyperpiesis: (1) I have given reasons (2) to believe that the pressure in the retinal arteries is not increased in arterio-sclerosis. (2) A marked increase in the number of haemorrhages is not infrequent towards the end of the patient's life when there is no corresponding increase of blood pressure. (3) Retinal haemorrhages are exceedingly common in leukaemia, pernicious anaemia, and rapidly produced secondary anaemias in which there is certainly no increase of blood pressure.

Types of haemorrhages. All haemorrhages of whatever type are much the most common over the central regions of the retina.

Small haemorrhages. These are usually flame-like and are situated in the nerve fibre layer; others, however, are more or less rosette shaped and are then probably in the inner granular layer—they are almost always multiple and probably occur by diapedesis. In the course of some weeks, the time varying with their size and density, they disappear and leave no trace behind, nor any discoverable defect of vision (Fig. 6). They undergo no intermediate changes in colour or appearance as absorption progresses, but simply fade away; they cause no symptoms unless the macula is involved. As individual haemorrhages become absorbed fresh ones may appear, so that a crop of haemorrhages, in various stages of absorption, may be present over a period of many months or several years.

Single large haemorrhages. These may be many times larger than the optic disk. They are, or soon become, heterogeneous in texture as seen with the ophthalmoscope, and have ragged and irregular, though well-defined edges. Intermixed with the blood areas of a pale colour are developed; they are no doubt a direct derivative of the blood. These large haemorrhages are probably due to a gross lesion of a vessel wall and not to diapedesis; seeing however that the blood remains interspersed among the surrounding tissues the damaged vessel is hidden.

It sometimes happens, however, that the blood, instead of infiltrating the tissues of the retina, comes to lie between it and its internal limiting membrane, and so drains away from the leaking vessel, rendering the actual lesion visible. These haemorrhages are slow to clear, as is to be expected from their large size; after clearance their former site may show no sign of their previous existence, although for a long time a few spots or flakes of blood remain.

Fig. 5 represents a haemorrhage of this type seen on Jan. 16, 1914,

in Case 21, Table A. On March 4, 1916, all traces of the haemorrhages (except for four or five minute spots of blood towards the periphery) had disappeared, and the area of the fundus previously involved showed no sort of abnormality to ophthalmoscopic examination. The small artery and vein which were lost to view in the haemorrhage were now plainly seen, but it was not possible to be sure which of them, if either, had been the source of the previous haemorrhage. The artery showed signs of very severe disease, but both vessels contained circulating blood and neither showed evidence of a lesion of its coats.

It sometimes happens that the blood bursts through the internal limiting membrane of the retina and infiltrates the vitreous body, producing sudden and severe loss of vision and leaving permanent dust-like opacities in the vitreous.

I believe it may be said of retinal haemorrhages in general, that they become absorbed in time, the period required varying with their size and density, and that they usually leave no trace behind them. In the case of a large haemorrhage a few spots of blood remain for a long time, and not infrequently a number of minute bright dots scattered thinly over the area.

Arterial Disease as a Cause of Optic Atrophy.

Curtailment of the blood supply to the retina, with impairment of sight and partial or complete atrophy of the optic nerve, may be brought about in two ways as a result of arterio-sclerosis. Thus (1) thrombosis of a diseased artery may occur, with sudden and irremediable loss of sight and subsequent optic atrophy, or (2) the sclerosis of the arteries may gradually attain such a degree, that they are no longer able to transmit sufficient blood for the needs of the tissues. In this latter case there is a gradual deterioration of vision with irregular contraction of the visual fields, and a varying degree of atrophy of the optic nerve. It is proposed to consider these two groups of cases separately.

1. *Thrombosis of the retinal artery or its branches.* Thrombosis of the central retinal artery, or of one of its branches, may occur in any case of severe retinal arterio-sclerosis, and whilst it would seem likely that those cases in which irregularity of the arterial lumen is marked would be specially prone to this accident, I have no evidence that this is so.

The signs of thrombosis are very striking and characteristic, the chief being sudden loss of sight, the signs of coagulation necrosis over the central regions of the fundus, and a ' cherry red spot ' at the macula. These cases are sometimes not differentiated from cases of embolism of the central artery. It is rather common to hear, after the initial sudden blindness, that there is a temporary partial recovery, followed in a few hours by recurrence of blindness which is complete and permanent.

In Table C particulars are given of nine patients to whom this accident happened. It will be seen that all had a high blood pressure, the average for seven

being 225 mm. Hg. There can be no doubt that thrombosis in these cases is largely dependent upon the diseased condition of the vessel walls, aided perhaps by a low local blood pressure. Five of the cases in Table C awoke in the morning to find themselves blind, and it seems reasonable to suppose that the lowered blood pressure during sleep was immediately responsible for the thrombosis. I have also reported a case (3) in which thrombosis occurred during a somewhat prolonged general anaesthesia. In this group atrophy of the retina and optic nerve follows, and the blindness is permanent and essentially complete.

2. *Gradual deterioration of sight and optic atrophy as a result of progressive sclerosis of the arteries of the retina.* Under this head we have to consider a group of patients in whom sclerosis of the arteries gradually attains such a degree, that without any sudden interference with the retinal supply this supply is slowly and gradually reduced to a point where it is no longer sufficient for the needs of the retinal tissues, and a slow progressive atrophy results. Such cases may of course culminate in sudden thrombosis as in the previous group. In Table E particulars of eight patients are given in whom partial atrophy followed from this cause.

Characteristics of this group. All are the subject of severe arterio-sclerosis and marked disease of the retinal vessels. One patient only in Table E had a blood pressure of less than 200 mm. Hg.: and the average pressure was 227 mm. Hg. The loss of sight is gradual, developing in the course of several weeks or months, and contrasts with the sudden loss which occurs in the previous group; in general too it is less severe.

Ophthalmoscopic changes. Evidence of disease of the retinal arteries is always well marked (Figs. 2, 3). The cherry red spot at the macula with the surrounding area of coagulation necrosis is not seen. In the early stages some oedema of the disk is present; later this is followed by a varying degree of optic atrophy.

It is necessary to consider the relation which the oedema of the disk, the optic atrophy, and the vascular disease bear to each other. Of the cases in Table E, four certainly and probably five showed some evidence of oedema of the disk, and it seems probable that this occurs at some stage in all this class of case. The oedema which occurs, however, is mild in degree; there is no marked swelling, dilatation of the small vessels, evidence of obstruction to the main vein, nor areas of exudate. The appearances then do not simulate the papilloedema of increased intracranial pressure, and a consideration of the following facts makes it clear that it is not a manifestation of some general nervous disease. (1) One disk only may be involved (Cases 1 and 3), and the other affected later or not at all. In Case 1, Table E, the right disk was pale and swollen in March, 1909, and the left was then normal (Mr. Holmes Spicer). In September, 1913, a similar change developed in the left eye. The patient is now alive and in fair health (March 4, 1916). (2) Of the 8 patients in Table E, 4 are still alive, 3 died of cerebral haemorrhage, 1 died of renal disease. None of them, therefore,

has died of a nervous disease, of which the papilloedema might be considered a part.

Visual fields. The visual fields undergo constriction which, as is to be expected, is quite irregular in type (Charts 1 to 7).

It should be pointed out here that in Case 3, Table E, the oedema of the disk was observed seven weeks before the patient was aware of any defect of sight, and in Case 6, Table E, oedema of the disk was noticed for nine months without the sight being sensibly affected.

In other cases the patient is first seen when some degree of optic atrophy is present, and, if this is bilateral, it may be that only by a consideration of the history of onset in the two eyes (an interval of months or years intervening between the onset in them), the type of atrophy, the presence of severe arterio-sclerosis, and the condition of the retinal arteries, is the true nature of the change discovered. The atrophy which occurs has the characters of a secondary rather than a primary atrophy ; the greyish colour, with shallow cupping and clear exposure of the lamina cribrosa, does not result, but a more opaque white disk, with an edge which, whilst it is not greatly blurred, yet lacks the very sharp definition of the primary atrophy of general paralysis or tabes dorsalis. In some cases a branch only of the artery may undergo extreme changes with a corresponding defect of vision.

I believe, then, that sclerosis of the retinal vessels may attain such a degree that they are no longer able to transmit an efficient supply of blood to the tissues, and that this slow starvation produces the defects of vision and oedema and atrophy of the optic nerve.

Lenticular Opacities.

With regard to arterio-sclerosis as a cause of lenticular opacities Gunn states : ' I have been impressed by the frequency of lenticular opacities in eyes showing these changes; should there be any connection between the two it would point probably to the ciliary arteries being involved.' I have not kept accurate records as to the incidence of lenticular opacities ; they are, of course, exceedingly common in patients past middle age, so that without a carefully compiled control series it would not be possible to state whether arterio-sclerosis does or does not predispose to their occurrence. My general rather strong impression is that there is no relation between the two.

Sex Incidence of Severe Retinal Arterio-sclerosis.

Both Nettleship and Gunn have recorded their opinion that retinal arterio-sclerosis is seen more often in the female sex, and my own impressions are in accord with theirs. A consideration of the present cases lends support to this opinion in the following particulars : (1) Of the 66 patients in Tables A and B,

36 were females and 30 were males. (2) The average systolic blood pressure for the females was 220 mm., and that for the males 210 mm. (3) Of 31 females, 20 are known to be alive and 11 have died ; of 24 males, 11 are known to be alive and 13 have died. (4) The following are the ten cases with the highest individual blood pressures :

Females.		*Males.*	
Blood Pressure.		Blood Pressure.	
Case 60	300 mm.	Case 46	265 mm.
,, 43	290 ,,	,, 33	253 ,,
,, 11	270 ,,	,, 8	250 ,,
,, 19	260 ,,		
,, 39	255 ,,		
,, 2	250 ,,		
,, 23	250 ,,		

Case 60, Table B, was first seen in May, 1913, and she had at that time a systolic blood pressure of greater than 300 mm. Through the courtesy of Dr. Brander, I was enabled to examine her again on June 2, 1916, in the Hackney Infirmary. She had had a stroke two years ago, but whilst in poor health she is not bed-ridden ; she is nearly blind, and the retinal vascular disease is extreme in degree. Her systolic blood pressure is 290 mm. This woman's blood pressure was greater than 300 mm. in May, 1913 ; it was then taken at monthly intervals for six months, and on one occasion only was it less than 300 mm. In spite of two years' removal from ordinary sources of anxiety and physical exertion, a considerable part of which time has been spent in bed, her systolic blood pressure remains at almost the same level, and there can be no doubt that it had been as high as 300 mm. for some time, perhaps several years before she first came under observation.

These observations seem to indicate that women are more tolerant of a high blood pressure than men : for (1) the average systolic blood pressure was 10 mm. higher in the females ; (2) 35 per cent. of the females are known to have died, whilst 54 per cent. of the males are known to have died ; (3) of the 10 patients with the highest blood pressures 7 were women.

II.   ARTERIO-SCLEROTIC RETINITIS AS A CLINICAL ENTITY.

Considerations on the Pathology of Renal Retinitis.

In the previous section the signs of retinal arterio-sclerosis have alone been dealt with ; it is now proposed to consider a group of cases comprised in Table B in which a condition of retinal exudates has become engrafted on retinal arterio-sclerosis. It is hoped to show that this condition differs in a number of important particulars from renal retinitis, and that it is sufficiently distinctive to be worthy of separate recognition under the term 'arterio-sclerotic retinitis'.

In renal retinitis in general there are, I believe, two factors which are

responsible for the retinal changes, the one vascular and the other toxic; and according as the one or the other of these is the more prominent so will the retinal changes vary.   In chronic parenchymatous nephritis the vascular factor is much less prominent than the toxic, the blood pressure may not be greatly raised, and the retinal changes are characteristically those which I believe are indicative of a toxic element in the disease.   There are present numerous soft-edged areas of white exudate in the tissues of the retina which may, by con-fluence, give rise to large areas of infiltration in this structure.   These areas of exudate are variously described as ' cotton-wool patches ', ' soft-edged areas ', or ' snow-bank patches ', and are well recognized under these terms.   There is much oedema of the retina which may lead to its detachment (6).   Retinal haemorrhages are not very plentiful, but may often be seen to form a fringe around the areas of exudate and in part to overlie them.   The well-known star figure, owing to the copiousness of the exudate, and to the fact that this is not confined to Henle's layer, is seldom seen.

On the other hand, in the case of chronic interstitial nephritis with which a high blood pressure is always associated, the retinal vessels show signs of sclerosis, haemorrhages are more extensive and more plentiful, and the ' fish scale ' or ' mackerel back ' spots forming the star figure around the macula are frequently present.

Soft-edged areas of exudate (cotton-wool patches) are much less plentiful and never so extensive as in the former variety.

I believe that a vascular and a toxic element enter into the causation of both these varieties of retinitis, but that, whereas in the first variety the toxic factor is the more prominent, the vascular factor is more prominent in the second.

In arterio-sclerosis we have to deal with a disease of the small vessels, as was originally made clear by Gull and Sutton (7).   In this disease the vessels of the retina and of the kidney are affected, in common with many of the other small vessels of the body ; and the nutrition and functions of these organs are thereby impaired.   I believe that the retinitis which develops in such cases is solely due to the disease of the retinal vessels, and that it corresponds with the vascular moiety of renal retinitis ; but as the progress of the disease in the small vessels of the kidney may, in the course of years, so seriously involve the kidney substance as to lead to renal insufficiency, so there may coincidentally appear soft-edged areas of exudate in the retina, which are indicative of this insufficiency, and which may correspond with the toxic moiety of renal retinitis.   It is more than possible that the vascular disease itself is primarily due to the toxic products of perverted or incomplete metabolism.

The Characters of Arterio-sclerotic Retinitis.

Ophthalmoscopic.   It is to be understood that the changes to be described are always superadded to the signs of retinal arterio-sclerosis, which are usually well marked, and retinal haemorrhages therefore are almost invariably present.

The retinal exudates, the presence of which is taken to justify the term 'retinitis', as in the diabetic and renal form of disease, take the form of small white dots, spots, or small areas.   The dots or spots are irregularly circular in outline and vary a good deal in size, a large dot being equal in diameter to a large retinal vein.   They are sharply defined, there is no ophthalmoscopic evidence of surrounding oedema, and no pigmentary disturbance in their neighbourhood (Figs. 2, 3, 4, 8, 9, 10, 11, 12).   They are usually scanty and are never really copious.

Arrangement.   In some cases these dots can be seen to be arranged in relation with the radicles of the smallest veins, and whilst this is sometimes quite unmistakable (Fig. 8, Plate 4), in other instances no such arrangement can be made out.   It is somewhat common to find a group of them between the macula and optic disk (Figs. 2, 4, &c.).   In other cases they constitute a complete, or much more often a partial, star figure around the macula (Fig. 9).

Changes in these dots.   These dots are very chronic in nature, they are slow to develop, and are very slow to undergo change.   It is undoubtedly true that they may persist for some months without undergoing any marked change ; if, however, they are watched by means of carefully drawn plans, it will be found that they undergo changes in shape, that two closely adjoining dots may rarely become confluent, and that they may *completely disappear and leave no trace behind them*.   Thus in Case 55, Fig. 4, the dots had completely disappeared, leaving no trace behind them in the course of three years ; in Case 59, Fig. 8, all had disappeared two years later; and in Case 53, Fig. 9, the partial star figure composed of these dots had almost completely disappeared in seven months, and two years later no trace of them was to be found.   In many other cases I have watched individual dots or groups of dots disappear in the course of several months.

In addition to these discrete dots, other larger areas or small plaques are seen in the more advanced cases.   They occur in the central regions and are never very large nor very plentiful.   In general characters they appear to be identical in nature with the discrete dots, i. e. they have a hard edge, are dirty white in colour, are irregularly circular or oval in outline, have no obvious oedema surrounding them, nor is there haemorrhage or pigmentary disturbance in relation with them.   They are slow to undergo change, and after some time may develop cholesterin crystals within them.   They do not appear to be formed by conglomeration of the discrete dots (Fig. 10).

Pipe-stem sheathing of arteries.   In some cases the arteries develop a white plaque-like deposit apparently within their perivascular sheaths.   Sometimes this completely surrounds the vessel for a longer or shorter length of its course, giving the appearance of a pipe-stem.   The exudate is very white and solid looking, having sharp-cut edges ; it starts and ends quite abruptly.   The breadth of the blood-stream as it enters and emerges in such case is quite unaltered, and, contrary to what might be expected from their solid appearance, these plaque-like deposits may completely disappear and leave no trace behind.   In Case 50,

Table B, Fig. 13, this solid looking plaque-like sheathing disappeared completely and left no trace in the course of nine months.

The condition has been described by Hulke (8). It is to be noticed that it differs entirely from the conversion of the arteries into white threads with narrowing or disappearance of the blood-stream, for the width of the blood-stream on each side of the plaque is of full breadth, and, as stated, the plaque may completely disappear and leave no sign behind it.

Unilaterality. It is common to find that whilst evidences of arterio-sclerosis are almost invariably well marked in each eye, the changes which have just been described are present in one eye only. Thus of the thirty-one patients in Table B in whom these characters were present they affected one eye only in fourteen instances (45 per cent.).

I wish to make it plain that it is not suggested that the individual forms of exudate here described are of themselves distinctive or pathognomonic, for individual dots and areas of exudate of a character which is indistinguishable from them, at any rate ophthalmoscopically, are to be seen in cases of renal and diabetic retinitis, retinitis circinata, and other conditions. It is their scantiness, their arrangement, their course, and the fact that they are always engrafted on a condition of severe arterio-sclerosis, which combine to form a characteristic ophthalmoscopic picture.

Histological characters of the exudate. Fig. 18 represents a section through several of the discrete degenerative dots which were identified during life. They are placed entirely in the internuclear layer, and are composed of round or oval masses of exudate, which is perfectly homogeneous and hyaline in appearance ; it is stained pink or pale heliotrope in haematoxylin and eosin sections, and is especially deeply stained by orcein. Some of these round or oval bodies have an appearance as if they had separated out from a mass of less dense hyaline material in the midst of which they lie. I do not think this exudate can be distinguished from that seen in some cases of renal retinitis, and it is probably of the same nature though much less abundant. None of the large phagocytic cells were found which surround the hyaline exudate and form so conspicuous a feature in many sections of renal retinitis, and since it is in these cells that fat occurs almost, if not quite, exclusively in renal retinitis (Fig. 21), no fat was discovered in the present cases.

When the retinal changes have persisted for some time a few soft-edged areas may make their appearance. These were present in the case from which Figs. 16, 18, 19 were obtained. The following is the note I made of them during life : 'There are two soft-edged areas, which are much larger than the degenerative dots ; they are of a pale buff colour, have ill-defined edges, and in one place retinal vessels pass over them unobscured.' The rough outline, Fig. 22, was made in order to identify the areas in the histological specimens, and the artery and vein are seen in many of the sections of this area.

These areas were due to a conversion of the nerve fibre layer into a sort of coarse sponge-work, the spaces apparently being occupied by fluid ; the tissues

themselves appear to be undergoing hyaline change (Fig. 19). It will
be seen that these areas are distinct histologically from the 'cotton-wool'
patches and the exudate which forms the star figure in renal retinitis, and from
the degenerative dots already described. Gangliform degeneration of the nerve
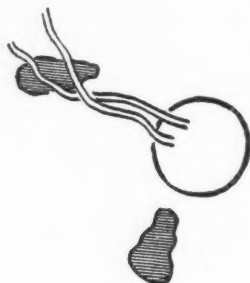
FIG. 22.
(For description see Text, p. 43.)

fibre layer was present in Case 52, Fig. 20; it occurs also in renal retinitis
(Mawas (9)) and other conditions, and whilst it seems likely that it is dependent
upon deficiency of blood supply due to the disease of the vessels, confirmation of
this is lacking, and the change cannot be considered as characteristic of arterio-
sclerotic retinitis.

Evidence for the Differentiation of Arterio-sclerotic Retinitis as a Clinical Entity.

We have now to consider in detail the grounds upon which this combination
of vascular disease with the exudates in the retina which has been described
is to be looked upon as being a distinctive condition and separated from renal
retinitis. It need hardly be stated that it is not contended that there are hard
and fast lines which sharply differentiate the two conditions. The question will
be considered under the following heads:

Ophthalmoscopic appearances. (1) The sclerosis of the retinal arteries is
always a precursor to the development of the exudates, and consequently
evidence of this is always well marked. In renal retinitis vascular disease is
usually present; it is, however, less marked, and the evidences of it are apt to be
marked by the other manifestations of retinitis. (2) Retinal haemorrhages tend
to be smaller and more scattered than in renal retinitis. (3) The retinal exudates
which have been described are to some extent distinctive in appearance and
arrangement. (4) Patches of soft-edged exudate (woolly patches, cotton-wool
patches, snow-bank or cumulus cloud exudate) are rare in arterio-sclerotic
retinitis, and when they occur are probably evidence of beginning renal
insufficiency. (5) General retinal oedema does not occur, and consequently
retinal detachment is rarely, if ever, produced. (6) The star figure may be

present in either case. It is to be remembered that the arrangement of exudate in the retina in the form of a complete or partial star figure is dependent upon an anatomical basis, and consequently is of no distinctive value. Thus it may be seen in such widely differing diseases as papilloedema, thrombosis of the central retinal vein, diabetic retinitis, &c. The distinctive features concern the appearances of the exudate which composes the star figure. In arterio-sclerotic retinitis it is composed of the small dots already described (Figs. 4, 8, 9, &c.). In renal retinitis the dots are larger and more elongated in the line of the ray of the star; they are less discrete from the first, and tend to coalesce to form ragged and irregular rods. Ophthalmoscopic evidence of oedema is usually present, and, as the disease progresses, the star arrangement is often obscured as a result of coalescence and conglomeration of the exudate. (7) It has been already stated that in 45 per cent. of the thirty-one patients in Table B the retinitis was unilateral. Renal retinitis may be evident in one eye before the other, but it seldom remains unilateral for more than a few days or weeks.

Evidence of the Evolution of Arterio-sclerotic Retinitis from Retinal Arterio-sclerosis.

If it be true that arterio-sclerotic retinitis is evolved from a condition of retinal arterio-sclerosis, and is to be looked upon as a further advanced degree of the disease, it should be possible to watch this evolution in an individual case; and the comparison between a group of patients suffering from retinal arterio-sclerosis (Table A) and a group in whom arterio-sclerotic retinitis was present (Table B) should make it clear that the latter group were suffering from the same disease as the former in a more advanced stage.

A. *The gradual evolution of arterio-sclerotic retinitis in an individual.* It is not often that one is able, in an individual case, to watch the gradual development of arterio-sclerotic retinitis from retinal arterio-sclerosis. Gunn (10) gives particulars of a patient whom he was able to watch over a period of ten years.

The patient, a woman, was seen by him at the age of 51; she then had a little haemorrhage into the vitreous of one eye, and bright retinal arteries. She had no albuminuria nor renal symptoms. At the age of 56 she developed retinal haemorrhages, and albumin was occasionally present in the urine. From 58 to 59 she had further retinal haemorrhages, developed retinal patches, and had a cerebral seizure. Albumin was now found more frequently in the urine. At the age of 61 (ten years after being first seen) the retinitis was worse; she showed signs of cerebral degeneration, and developed some uraemic symptoms. Gunn states, 'I anticipate that other such cases followed up will be forthcoming'.

I have watched the retinal exudates develop in cases showing arterial disease only; I have also watched the disappearance of these exudates (*vide supra*) so as to leave no trace of their former existence behind them. The best example that I have seen of the former is Case 54, Table B, which I give below in some detail. By a fortunate chance this patient was for some time under Mr. Gunn's care.

Annie H., aged 48.

1908. Nov. 28. 'Extensive arterio-sclerosis. Small haemorrhagic patches, one large haemorrhage absorbing. Veins sausage shaped owing to arterial pressure.' M. Gunn.

Urine, S. G. 1015. No albumin. No sugar.

1909. Feb. 20. *Urine*, S. G. 1015. No albumin. No sugar.

1910. Mar. 9. *Urine*, S. G. 1007. No albumin. No sugar.

1911. Jan. 28. 'Gross vascular changes. Many scattered haemorrhages. Ampulliform enlargement of veins. White glistening spots disposed radially round the macula.' G. Coats.

Urine, S. G. 1003. Moderate cloud of albumin.

1913. May 10. (I first saw the patient on this date.) *Urine*, S. G. 1006. Cloud of albumin. Retinal changes essentially as above. *Blood pressure*, 250 mm.

The patient was examined on the following dates, but except for small changes in the individual areas of haemorrhage and exudate no essential change occurred. The changes in the haemorrhages and exudate were studied by means of outline drawings.

1913. May 23, June 16, 23, and 30, Sept. 13, and Dec. 13.

1914. Jan. 24, Mar. 28, Nov. 15.

1915. Feb. 20, Aug. 28. On this last date she was looking very well; she had no oedema or headaches.

Ophthalmoscopically.

R. E. Degenerative dots with very little tendency to confluence are scattered somewhat thickly over the central region. There is no atrophy. Evidently of different significance from renal retinitis.

Blood pressure, 243 mm. *Urine*, S. G. 1006. Cloud albumin. No sugar.

L. E. Vessels very bright and sclerosed. White degenerative dots having a slight tendency to a star arrangement, but for the most part scattered freely over the central region.

1916. Mar. 30. There is no essential change in her condition and she is in very fair health.

May 15. She is still fairly well.

This patient has been under more or less constant observation for more than seven and a half years. At first the retinae exhibited the changes of arterio-sclerosis only, and at this time her urine was of a normal specific gravity and contained no albumin (Marcus Gunn). Two years and three months later (Jan. 28. 1911) the first signs of retinal exudates (arterio-sclerotic retinitis) were seen, in the form of glistening spots around the macula (George Coats), and her urine was now of low specific gravity (1003) and contained albumin for the first time.

Since that time up to the present (June 15, 1916) I have had her under constant observation. Her urine remains of low specific gravity and usually contains albumin.

Her blood pressure was first taken on May 10, 1913, when it was 250 mm.; since that time it has been as low as 185 mm.; when last taken, Aug. 28, 1915, it was 243 mm.

The fundi still show signs of severe arterio-sclerosis, and numerous dots and

small areas of hard-edged white exudate : there are no woolly patches present (Figs. 10, 11).

This patient, then, has had 'arterio-sclerotic retinitis' for five years, and by means of the development of fresh haemorrhages and fresh areas of exudate, as the older ones have become absorbed, the general appearance of the fundi has changed but little during this time.   There have been no soft-edged areas or woolly patches such as develop with renal insufficiency, and I believe the whole of the local retinal changes are due to the vascular disease.   I expect this patient will die of heart failure if she escapes a cerebral haemorrhage.

B. *A comparison of a group of patients in whom retinal arterio-sclerosis was present (Table A) with a group in whom 'arterio-sclerotic retinitis' was present (Table B)*.   Tables A and B comprise patients in whom retinal arterio-sclerosis was present, but whereas retinal exudates were present in addition, in one or both eyes in Table B, none were present in the patients in Table A.   If then the former condition is evolved from the latter as a result of the further progress of the arterial disease, an analysis of the patients in the two groups should lend support to the view that those comprised in Table B are suffering from the same disease as those in Table A, but in a further advanced stage.

The following abridged analysis demonstrates the relationship of these groups to each other, in several important particulars :

Abridged Analysis of Patients comprised in Tables A and B.

	Table A. Retinal Arterio-sclerosis.	Table B. Arterio-sclerotic Retinitis.
Number of patients	35	31
Average age	59	59
Average systolic blood pressure	211	222
Albumin constantly present in the urine	6 out of 17	9 out of 17
Present condition	8 are known to have died 19 are known to be alive	16 are known to have died 12 are known to be alive
Evidence of gross cerebral vascular lesions	Present in 11 Absent in 13	Present in 11 Absent in 9

The chief points brought out here are the higher blood pressure, the higher mortality, and the greater incidence of gross vascular cerebral lesions in those in whom arterio-sclerotic retinitis was present.

C.   *Length of Life and Manner of Death of the Subjects of 'Arterio-sclerotic Retinitis'.*

Length of life.   It is in general true that few patients live so long as two years after the discovery of renal retinitis, and a large proportion of them die from uraemia.   On the other hand, of the present patients with 'arterio-sclerotic retinitis', 10 females out of 17 are alive on an average 3 years and 5 months after the onset of symptoms, and 2 males out of 11 are alive 2 years and

10 months after the onset of symptoms.   This length of time of survival is more significant from the fact that the patients had already attained a considerably advanced age.

Manner of death.   Seventeen patients are known to have died, and of these seven certainly died of a cerebral haemorrhage, whereas in two cases only is uraemia given as the cause of death.   I do not forget in this connexion that the subjects of chronic interstitial nephritis frequently die of cerebral haemorrhage.

Summary.

I believe then, for the following reasons, that there is a form of retinitis which is associated with severe general arterio-sclerosis ; that it is caused by the local retinal vascular disease ; and that its association with disease of the kidney is only incidental.

That the retinitis is in large measure distinct from renal retinitis in its ophthalmoscopic characters, in its significance, and in its prognostic value.

1. It is always associated with severe general arterio-sclerosis and retinal vascular disease.

2. Its gradual evolution from a condition of retinal arterio-sclerosis can be traced.

3. The ophthalmoscopic appearances are in large measure distinctive ; it is frequently unilateral, and cotton-wool patches never occur.

4. The tenure of life of the subjects of this condition is very uncertain, but they often live a number of years.

5. The cause of death is referable to disease of the vascular system and not to disease of the kidney.

I suggest that this form of retinitis calls for separate recognition.

III. The Relation of Sclerosis of the Retinal Arteries to Cerebral Arterio-sclerosis.

From the manner of development of the retina and the source of its blood supply, it is to be expected that disease of its vessels will be similar in kind, and perhaps in degree, to that of the vessels of the brain.   When in addition it is remembered that the retinal vessels can be examined in their natural condition during life under a magnification of 15 diameters (direct ophthalmoscopy), it is clear that the investigation of the relation between the ophthalmological evidence of retinal vascular disease and the manifestations of cerebral vascular disease is one of much importance.

In order to obtain as complete and accurate an idea as possible of the relation between these two conditions, I have investigated the subject from two

directly opposite aspects. Thus, on the one hand, I have examined the fundi of 44 patients who were admitted to the wards of St. Bartholomew's Hospital suffering from hemiplegia of sudden onset, which was diagnosed by the physician under whose care the patient was admitted as being due to either a cerebral haemorrhage or to cerebral thrombosis (Table D). In some of these cases a post-mortem examination has been made.

On the other hand, I have investigated a group of 66 patients who have attended at the Moorfields Eye Hospital on account of impaired vision, which has been due to the results of retinal arterio-sclerosis (Tables A and B). I have not thought it necessary to trace further the first group, as they were all of them already the subject of a gross cerebral vascular lesion. Those of the second group, however, I have examined at regular intervals, and have endeavoured to keep them under observation up to the present time or to the time of their death. In this last event I have, where possible, discovered the immediate cause of death. It is proposed to consider these two groups separately.

A. *The evidence of retinal arterio-sclerosis in patients suffering from cerebral haemorrhage or thrombosis.* These patients are included in Table D, where short particulars of them are given: they are 44 in number. The ophthalmoscopic examination only has been carried out by myself. In some cases, especially where death is approaching, the secretion or collection of mucus in the conjunctival sac renders it impossible to obtain a clear view of the fundus, and some cases have had to be discarded on this account.

It will be seen that of these 44 patients, 31 were males and 13 females, and 28 (out of 44) were between the ages of 50 and 70. The systolic blood pressure was available in 30 instances, and in 15 of them it was higher than 200 mm. Hg. The results of the ophthalmoscopic examination are included in columns 7 and 8. In column 7 the condition of the arteries is indicated, varying from natural (nat.), through $\frac{\pm}{2}$, +, to + +. The grounds upon which these estimates are based have already been fully discussed (Section I). In addition to the disease of the vessels, there was in four cases either pallor or oedema of the disk; and in eight cases areas of exudate in the retinae were present, constituting a condition of ' arterio-sclerotic retinitis ' (Section II).

The incidence of the varying degrees of retinal arterio-sclerosis may be tabulated as follows:

No Evidence of Disease.	Evidence of Mild or Moderately Severe Disease.	Evidence of Severe Disease including ' Arterio-sclerotic Retinitis '.
13 (30 %)	12 (27 %)	19 (43 %)

Similar observations to the above were carried out by Gunn (10). He examined 17 patients in the National Hospital for Nervous Diseases on one day, 7 males and 10 females. All were suffering from hemiplegia of sudden onset,

presumably due to vascular disease. Seven of them showed perfectly definite retinal vascular changes, three showed slight vascular changes, and seven showed no decided retinal changes. Thus of my own cases 70 per cent. and of Gunn's cases 59 per cent. showed definite evidence of retinal vascular disease.

B. *Evidence of cerebral vascular disease in patients who have sought advice on account of symptoms directly due to retinal arterio-sclerosis.* These patients are 66 in number. They have for the most part been examined at regular intervals over considerable periods and the present state of 59 of them is known. The evidence of cerebral vascular disease is of two kinds : (1) the history of attacks to be obtained from the patients or their friends ; (2) the cause of death where this has occurred.

As regards the history I propose to concern myself chiefly with symptoms which are clearly referable to a *gross* vascular lesion, either a haemorrhage or thrombosis ; it is, however, worth considering for a moment certain symptoms which are so frequent as to be usual, and which are no doubt due to the diseased condition of the cerebral vessels.

I have elsewhere given reasons for believing that the pressure in the small arteries in arterio-sclerosis is, at any rate in some cases, less than the normal, in spite of a systolic pressure in the large arteries which is greatly raised, and it seems likely that this fact, combined with the narrowing and loss of elasticity of the vessel walls, is responsible for a very inefficient circulation to the tissues, and accounts for many of the minor symptoms of which arterio-sclerotic patients complain.

It seems probable that the symptoms indicated by the following remarks which have been made to me are to be explained in this way : ' I seem to have lost all energy ', ' I seem to have no strength ', ' I keep forgetting myself', ' I lose myself completely at times ', &c., &c. It is common, too, to find that the adjustment of the circulation on lying down and rising up is much impaired. I have made particular inquiry as to the existence of headaches in 35 patients (13 males and 22 females). The average systolic pressure in both males and females was 216 mm. Hg.

Six of the 13 males and 12 of the 22 females stated that they did not suffer from headaches. Five patients stated that they used to have them, but did not have them now. In some cases they were described as being ' shocking' or ' very bad '. It will be seen that more than a half (18 out of 35) of the patients with an average blood pressure of 216 mm. Hg. stated that they did not suffer from headaches, and it is to be noted that this was in reply to an inquiry which necessarily took the form of a leading question.

Evidence of the occurrence of GROSS *vascular lesions.* The manifestations of cerebral haemorrhage or thrombosis may range from death or hemiplegia to the temporary loss of power in limbs, speech, or senses in all their varying degrees. In 46 cases there is satisfactory evidence as to the development or otherwise of such a lesion. Cases 32, 40, 53, 55, 57 are considered as unsatisfactory and are therefore omitted. I do not propose to differentiate here between those suffering

from retinal arterio-sclerosis and those with 'arterio-sclerotic retinitis'. This has been done in the analyses of Tables A and B, and it will be seen, as has been stated, to lend support to the view that 'arterio-sclerotic retinitis' is a further advanced stage of retinal arterio-sclerosis. Of these 46 patients there was satisfactory evidence of the occurrence of a gross cerebral vascular lesion in 21. In 25 cases there was no evidence of any such lesion having occurred ; as, however, 18 of these 25 are still alive, there can be no doubt that a considerable proportion of these will develop such a lesion before they die.

Summary.

The evidence, then, as to the relation between the condition of the retinal arteries and that of the arteries of the brain would appear to be both striking and conclusive, for—

1. Of 44 patients suffering from a gross cerebral vascular lesion (Table D) 31 (70 per cent.) exhibited evidence of retinal vascular disease, and in 19 of them (43 per cent.) it was severe in degree.

2. Of the patients in Tables A and B 27 are known to have died, and the cause of death has been ascertained in 26 instances.

Of these 26 cases a gross vascular cerebral lesion has been the cause of death in 12 (46 per cent.).

3. Of the patients in Tables A and B, i.e. patients in whom retinal vascular disease was sufficiently severe to give rise to symptoms, there are 46 in whom there is satisfactory information as to the development or otherwise of gross cerebral lesions.

Of these 46 patients 21 (46 per cent.) had either suffered from such a lesion or developed one in the course of about three years, and as 18 of the remainder are known to be still alive there can be no doubt that the above proportion will be added to as time proceeds.

IV. Eight Cases illustrating Arterio-sclerosis as a Cause of Partial Optic Atrophy.

Case 1.   Emma C., aged 62, under the care of Mr. Holmes Spicer.
1909.   March 19.   *R. E.*   Failing one month.   Optic disk pale and swollen.
June 25.   *R. E.*   Disk very white, arteries very small.
1912.   June 14.   *R. E.*   A large island only of visual field (Chart 1).
L. E.   Field complete V = $\frac{6}{6}$.

RIGHT.
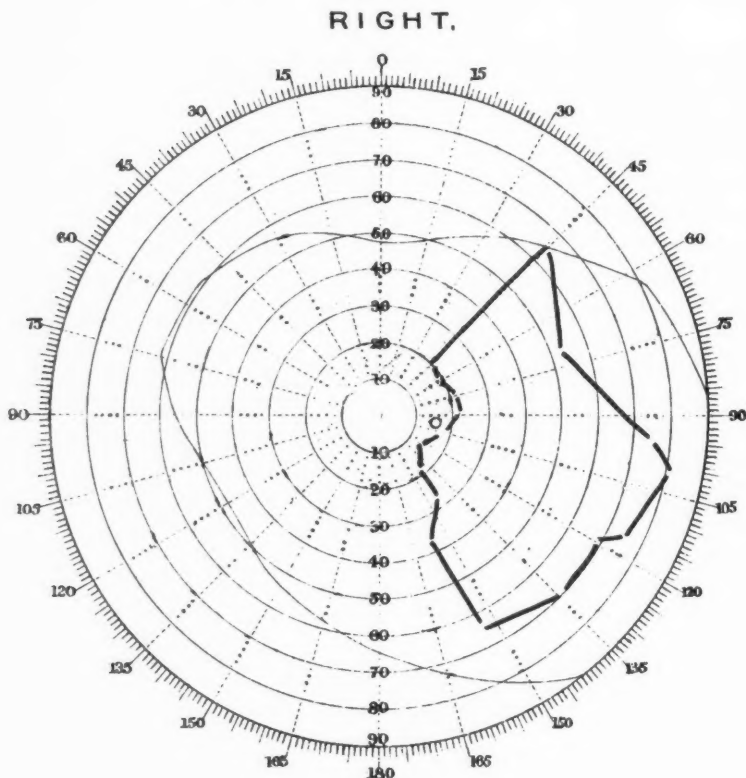
Chart 1.   Emma C., 8/9/13.

1913.   Sept. 8.   *L. E.*   Woke up one morning six weeks ago and found this eye misty.   It gradually got worse for about fourteen days.   It seemed to extend upwards from below till she was stone blind, since when some recovery has taken place.   V now = hand movements with each eye.   The outline drawing Fig. 1 was made on this date.   *Blood pressure*, 200.   *Urine*, S. G. 1008.   No albumin.
1916.   March 4.   Has been very ill, but is now much better.
R. E.   Disk very white and has the appearance of a secondary rather than

a primary atrophy. The arteries on the disk are very small, but when traced outwards appear to attain full size.

L. E. Disk very white, secondary atrophy. Vessels quite unaltered from appearances shown in Fig. 1, i. e. 2½ years ago. No haemorrhages or exudate. Veins of normal size. Visual field much reduced (Chart 2).

Case 2. Catherine Ann W., aged 71, under the care of Mr. A. C. Hudson. Her sight has been failing for some months.

1913. July 14. *R. E.* The arteries in part look normal, and then tail off into very thin lines, and again swell out to the normal size beyond. $V = < \frac{6}{60}$.
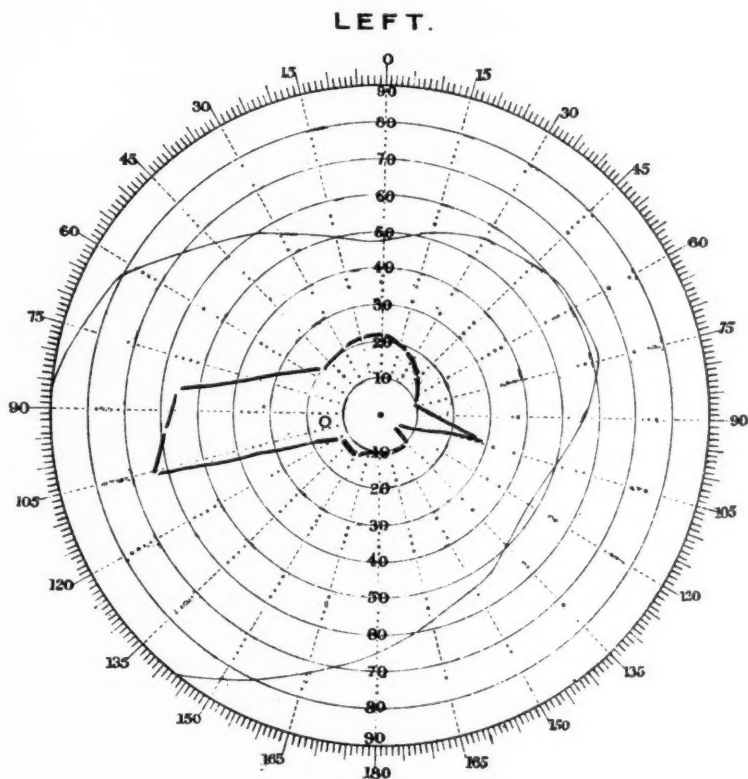
CHART 2. Emma C., 8/9/13.

L. E. Similar to the above, but arteries not so small. There is no gross lesion to account for the loss of sight. $V = \frac{6}{60}$. *Blood pressure,* 230. *Urine,* S. G. 1003. Cloud of albumin.

1915. Feb. 17. 'Cannot see at all at times, lose the use of my legs.'

May 15. Died. 'Interstitial nephritis and uraemia.' Dr. W. Brander.

Case 3. Harriet C., aged 54, under the care of Mr. George Coats.

1912. Dec. 12. Left eye has been misty for three months.

1913. May 1. *R. E.* Arteries very bright, a few degenerative dots. $V = \frac{6}{6}$. *Blood pressure,* 220. *Urine,* S. G. 1006. No albumin.

L. E. Disk pale and oedematous. Arteries show severe disease, a few degenerative dots are present.

July 12. *R. E.* As before. $V = \frac{6}{9}$. *Blood pressure*, 200.

L. E. Disk has the appearance of secondary atrophy.

Aug. 9. *R. E.* A conspicuous change has occurred since the last visit. The disk edges are much obscured, there is definite swelling, and the condition is one of mild papilloedema.

L. E. As before.

LEFT.
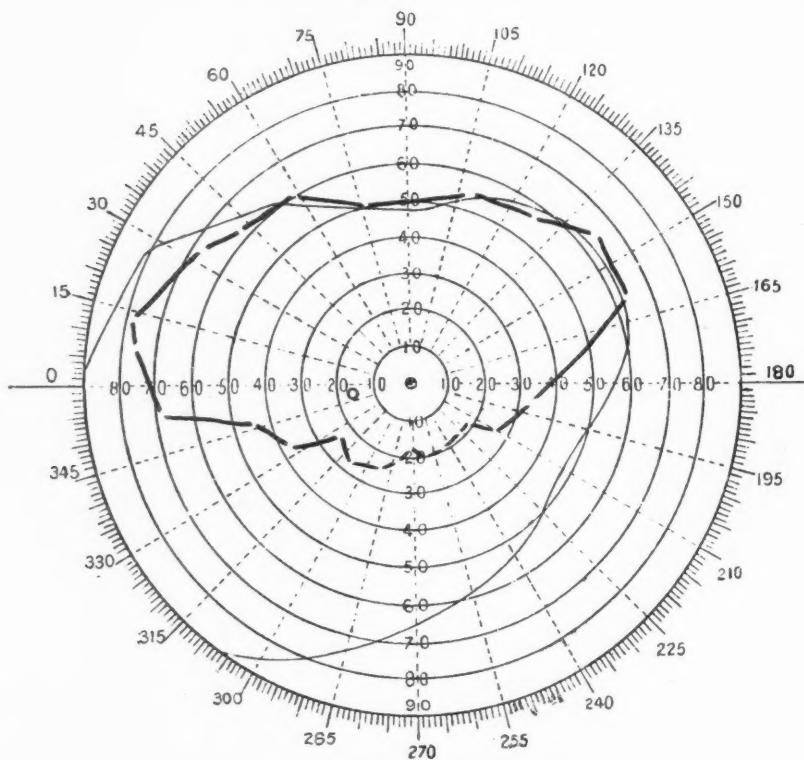
CHART 3. Harriet C., 11/10/13.

Oct. 11. *R. E.* One week ago the patient found she could not see with this eye. (N.B. Changes seen ophthalmoscopically on August 9.) Now well-marked papilloedema. There are a few degenerative dots, but no gross lesion. $V = \frac{3}{60}$. *Blood pressure*, 230.

L. E. Disk distinctly pale.

Nov. 8. *R. E.* Clearing $V = \frac{6}{60}$.

L. E. There is no doubt that the marked sclerotic changes in the upper artery and its branches, in the form of great reduction of lumen, are enough to account for the constricted field (Chart 3). $V = \frac{6}{60}$. *Blood pressure*, 225. *Urine*, S. G. 1015. No albumin.

1915. Feb. 17. 'Eyes not so well, has had congestion of the liver.'

Dec. 6. Died. 'Cerebral congestion with symptoms of effusion.' Dr. J. W. Davies.

Case 4.   Jane B., aged 45, under the care of Mr. Percy Flemming.
1913.   June 10.   Sight has been failing for a year.   Headaches.   No fits nor seizures.   *Blood pressure*, 245.   *Urine*, S. G. 1003.   Cloud of albumin.
R. E.   Vessels diseased, many haemorrhages. $V = \frac{6}{60}$.
L. E.   Arteries in places converted into white threads.   All vessels small. Disk very atrophic. $V = \frac{6}{60}$.
Nov. 11.   'Died of a cerebral haemorrhage.'   Dr. Kevern.
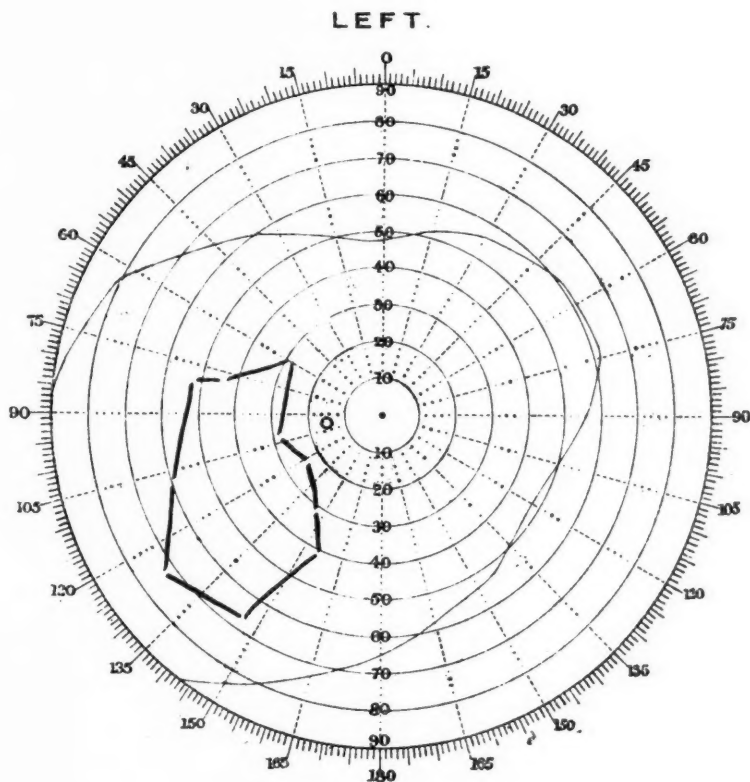
LEFT.

CHART 4.   John P., 11/3/14.

Case 5.   John P., aged 80, under the care of Mr. Holmes Spicer.
The left eye has been failing for five years, the right is now becoming misty. No cerebral attacks.
1914.   Feb. 3.   R. E.   Irregularity of lumen of arteries is exceedingly marked.   I saw nothing else gross.   Disk a little pale and hazy. $V = < \frac{6}{60}$. Visual field constricted (Chart 5).
L. E.   Disk pale.   Arteries small and in places converted into white threads. $V = < \frac{6}{60}$.   Visual field irregularly constricted (Chart 4).
1916.   March 14.   ' Is fairly well.'

RIGHT.
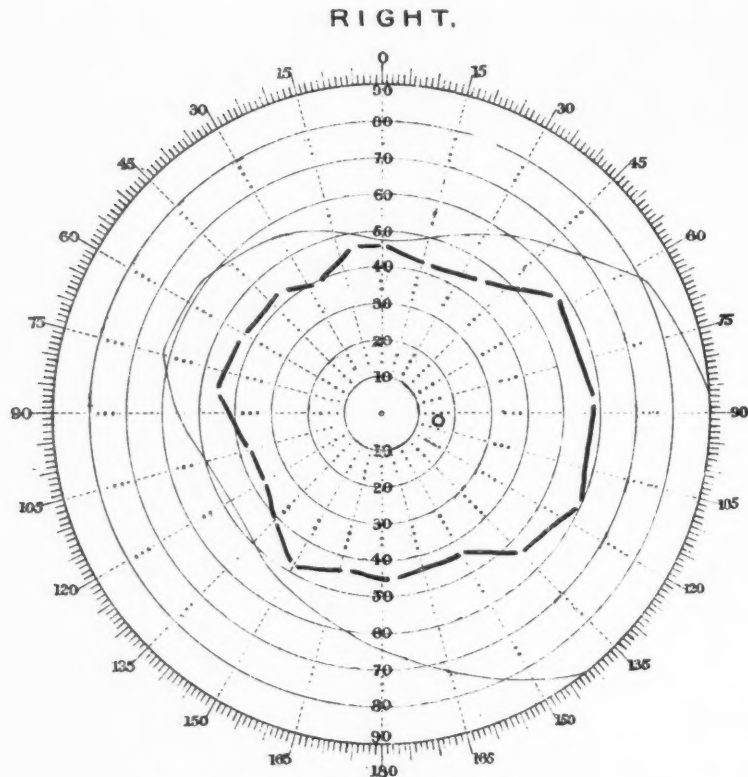
CHART 5. John P., 10/2/14.

Case 6. James G., aged 63, under the care of Mr. A. C. Hudson.
Sight failing two months.

1913. March 6. *R. E.* Disk oedematous and pale. Arteries somewhat small and of irregular calibre. Some retinal exudate. V = hand movements.

L. E. Well-marked oedema of disk. Haemorrhages and exudate present.

July 3. *R. E.* Disk now has the appearance of a secondary atrophy. *Blood pressure*, 250. *Urine*, S. G. 1002. Cloud of albumin.

L. E. Disk still oedematous. V = $\frac{6}{9}$.

Dec. 18. *R. E.* Essentially as above.

L. E. Still marked oedema of disk. V = $\frac{6}{9}$.

1914. April 14. 'Died in a fit.'

Case 7. William C., aged 48, attended at Moorfields under the care of Mr. Herbert Fisher.

His sight has been gradually failing for three months. No headaches nor cerebral symptoms, nor signs of tabes dorsalis.

1914. Jan. 6. Mr. Fisher's note : 'Optic disks pathologically pale, more so than an average toxic case. Some of the macular arteries are very strikingly bright and burnished and undoubtedly sclerosed. Many soft-edged ill-defined dots in central part of each fundus.'

March 13. *R. E.* The disk is pale, arteries exceedingly bright, burnished, of irregular lumen, and show marked irregularity of reflex. No haemorrhages. V = $\frac{6}{24}$.

L. E. The disk is paler than the right one and the arteries show an extreme degree of sclerosis. Visual fields complete. *Urine,* trace of albumin. *Blood pressure,* 195 mm.

1915. Feb. 18. *In statu quo.*

1916. March 12. Slight headaches. *Blood pressure,* 193 mm. *Urine,* S. G. 1010. Cloud of albumin.

RIGHT
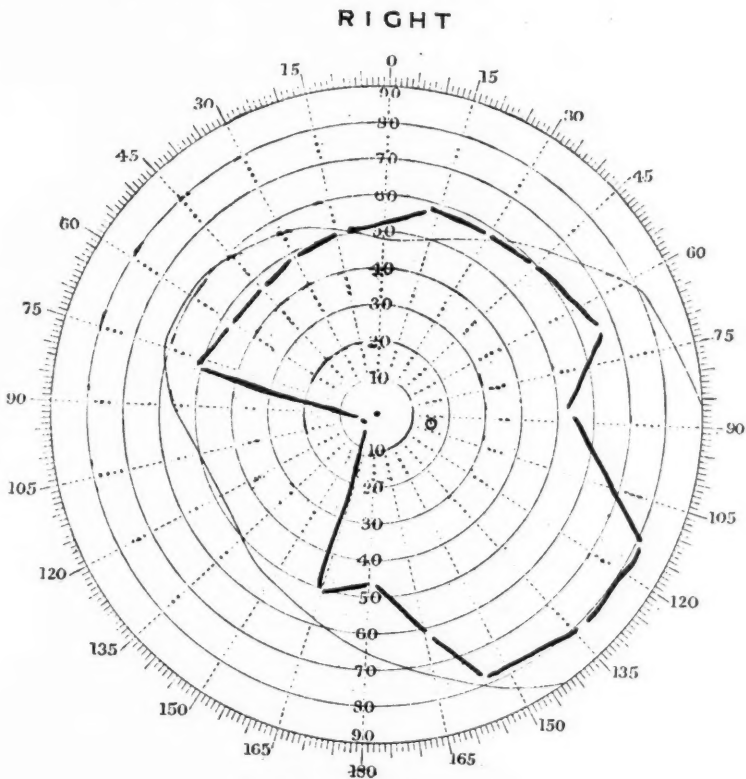
CHART 6. Richard H., 10/3/16.

Case 8. Richard H., aged 66, under the care of Mr. Herbert Fisher.

1914. March 23. Is in perfect health. No headaches or cerebral symptoms. The sight has failed gradually.

R. E. $V = < \frac{6}{60}$.

L. E. Disk pale. Arteries on disk very small, becoming larger with marked irregularity of lumen as they are traced outwards. $V = \frac{6}{6}$.

April 23. *R. E.* All arteries much diseased, upper temporal artery especially so, I think. *Blood pressure,* 265. *Urine,* S. G. 1021. No albumin.

1916. March 10. In very fair health. Short of breath. *Blood pressure,* 244. *Urine,* S. G. 1011. Haze of albumin.

R. E. Disk a little pale. The upper temporal artery is now converted into a white fibrous cord. Cf. note of April 23, 1914. Field of vision irregularly contracted (Chart 6).

L. E. Essentially as drawing made April 28, 1914 (Plate 5). The arteries are markedly irregular in calibre. Disk a little pale. No other lesion. Field complete. $V = \frac{6}{6}$.

TABLE A. Cases 1 to 35.

Patients in whom Retinal Arterio-sclerosis alone was present (i.e. Retinal Exudates were not present).

Blood Pressure. The figures represent in most cases the average for two or more readings.

Urine. The S.G. represents in most cases the average for two or more observations. The signs after alb. each represent a separate examination at intervals of one month: thus alb. + 0 means that on one occasion albumin was present and on a later examination it was absent.

Evidence of Gross Cerebral Vascular Lesions. Where this space is left blank it is indicated that no inquiry was made as to this point.

Present Condition. Where inverted commas are used the report has been obtained by letter or through a relative, otherwise it is implied that the patient was examined by myself on that date.

Period under Observation. This indicates the length of time between the first examination of the patient and the date under 'Present Condition or Cause of Death'.

Case No.	Name.	Sex.	Age.	Physician or Surgeon and Date of First Attendance.	Systolic Blood Pressure.	Urine, S.G. and Albumin.	Duration of Symptoms.	Period under Observation.	Retinal Changes. Degree of Vascular Disease.	Evidence of Gross Cerebral Vascular Lesions.	Present Condition or Cause of Death.	Reference to Figs.
1	Annie S.	♀	47	Dr. Morley Fletcher 24/7/13	240	1010 alb. +	$2\frac{7}{12}$	$2\frac{5}{12}$	severe	1911. A stroke. Right arm and leg useless, speech unintelligible, bed 6 weeks	*Died*, Dec. 24, 1915. 'Bright's disease; end came quite suddenly'	
2	Clara S.	♀	50	Mr. Devereux Marshall 18/10/13	250	1012 alb. + + + +	$1\frac{2}{12}$	$\frac{6}{12}$	very severe	none	*Died*, April 5, 1914. 'Bright's disease. Heart failure.' Dr. H. G. Barlow	
3	Louisa M.	♀	64	Mr. Holmes Spicer 9/4/07		1020 alb. +	$2\frac{7}{12}$	$2\frac{7}{12}$	very severe		*Died*, Nov. 25, 1909. Apoplexy	
4	Elizabeth C.	♀	66	Mr. Claude Worth 17/5/13	228	1017 alb. + 0 +	7	$2\frac{4}{12}$	moderate	none	*Died*, Sept. 22, 1915. (1) Myocarditis, (2) Gastritis. Dr. Rahilly	
5	David R.	♂	53	Sir Wilmot Herringham	220	1012 alb. +	$4\frac{5}{12}$	$1\frac{5}{12}$	moderate		*Died*, Dec. 16, 1915. Strangulated hernia. Dr. Welby Fisher	

No.	Name	Sex	Age	Surgeon / Date	B.P.	Urine	V. R.	V. L.	Retinitis	Symptoms	Remarks
6	Michael L.	♂	53		230	alb. +			moderate		*Died*, Nov. 14, 1915.
7	Robert D.	♂	58	Mr. Holmes Spicer 9/6/08		1009 alb. 0	$\frac{6}{12}$	$1\frac{1}{12}$	severe		*Died*, Nov. 15, 1908. Cardiac disease. Exhaustion Fig. 7
8	Walter W.	♂	66	Mr. Treacher Collins 23/10/13	250	1023 alb. + +	$1\frac{1}{12}$	$1\frac{5}{12}$	severe	One doubtful cerebral attack	*Died*, March 18, 1915. 'Cerebral haemorrhage'
9	Thomas B.	♂	55	Mr. Treacher Collins		alb. 0			moderate		*Died*, Dec., 1904. 'Cardiac disease.' Dr. T. E. Holman
10	Charles E.	♂		Mr. Treacher Collins		alb. +			severe		*Died*, Dec., 1906. 'Syncope. Heart failure.' P. M.
11	Sarah S.	♀	43	9/3/15	270	alb. + +			severe		*Not traced.* Death certificate has not been issued. *Registrar General*, June 30, 1916
12	Sarah A.	♀	55	Mr. A. C. Hudson 25/11/13	187	1007 alb. 0 0			severe	Three weeks ago she awoke to find she was numbed down the right side. At the end of 24 hours she could walk, the numbness had gone off. She is deaf in the right ear and has right homonymous hemianopia	*Not traced.* Death certificate has not been issued. *Registrar General*, June 30, 1916
13	Maria H.	♀		Mr. A. C. Hudson 24/2/13	160	1008 alb. 0 0			moderate		*Not traced.* Death certificate has not been issued. *Registrar General*, June 30, 1916

TABLE A (*continued*).

Case No.	Name.	Sex.	Age.	Physician or Surgeon and Date of First Attendance.	Systolic Blood Pressure.	Urine, S.G. and Albumin.	Duration of Symptoms.	Period under Observation.	Retinal Changes. Degree of Vascular Disease.	Evidence of Gross Cerebral Vascular Lesions.	Present Condition or Cause of Death.	Reference to Figs.
14	W. J. K.	♂	67		202	1011 alb. 0			moderate	none	*Not traced.* Death certificate has not been issued. *Registrar General*, June 30, 1916	
15	John C.	♂	46	Mr. Holmes Spicer					moderate		*Not traced.* Death certificate has not been issued. *Registrar General*, June 30, 1916	
16	Arthur R.	♂	55	Mr. A. C. Hudson 22/3/13	205	1015 alb. +			marked	Has had three fits of unconsciousness during the last three years	*Not traced.* Death certificate has not been issued. *Registrar General*, June 30, 1916	
17	Frances L.	♀	48	Mr. Treacher Collins 12/6/13	180	1002 alb. 0	$3\frac{3}{12}$	$2\frac{10}{12}$	mild		Complains that her nerves are in a bad way, but looks very well. 22/3/16	
18	Mary L.	♀	54	Mr. Herbert Fisher 30/8/13	225	1005 alb. + + +	$4\frac{6}{12}$	$2\frac{8}{12}$	severe	none	'Am keeping very well, but eyes are worse.' 15/3/16	
19	Sarah H.	♀	55	Mr. Herbert Parsons 2/4/13	260	1015 alb. + +	$3\frac{10}{12}$	3	severe	'Has had a partial stroke'	Sees fairly well with l. eye. R. eye enveloped in a thick mist. The stroke gradually passed off. At present is in fairly good health. 16/3/16	

No.	Name	Sex	Age	Examiner and Date		Urine			Severity	History	Remarks	
20	Clara P.	♀	56	Mr. Herbert Parsons 7/4/14	232	1020 alb. +	2	2	severe	none	No energy. Giddy on lying down, and at first on rising. Looks very well. 24/3/16	
21	Lettice C.	♀	56	Mr. Holmes Spicer 15/1/14	205	1010 alb. 0 0	$2\frac{5}{12}$	$2\frac{4}{12}$	moderate	none	Feels giddy at times, looks very well. 4/3/16	Fig. 5
22	Emma C.	♀	57	Mr. Holmes Spicer 8/9/13	218	1008 alb. + 0	7	$2\frac{5}{12}$	severe	none	Has been very ill, now much better; gets about fairly well. 4/3/16	Fig. 1
23	Martha L.	♀	60	Mr. Holmes Spicer 29/6/14	250	1006 alb. 0	$1\frac{9}{12}$	$1\frac{4}{12}$	severe	Hemiplegic attack. 24/1/16	Has not completely recovered from the hemiplegia. Gets about. 12/3/16	
24	Emily C.	♀	65	Mr. J. B. Lawford 27/9/13	188	1011 alb. 0	$2\frac{5}{12}$	$2\frac{5}{12}$	moderate	none	Is in perfect health. 24/3/16	
25	Ellen G.	♀	69	Mr. Worth 17/6/13	162	1007 alb. + 0 0	5	$2\frac{10}{12}$	mild	none	Looks very well indeed. Giddy. 13/3/16	
26	Emma P.	♀	70	Mr. Holmes Spicer 20/5/13	210	1018 alb. 0 0	$2\frac{11}{12}$	$2\frac{11}{12}$	moderate	none	Is very well. 4/4/16	
27	William C.		48	Mr. Herbert Fisher 13/3/14	194	1010 alb. + +	$2\frac{4}{12}$	$2\frac{1}{12}$	severe	Paralytic stroke all down right side, speech affected, laid up for 4 months	Is moderately well and is recovered from the stroke. 12/3/16	
28	George C.	♂	56	Mr. A. C. Hudson 22/1/14	170	1015 alb. 0	$2\frac{3}{12}$	$2\frac{2}{12}$	mild	none	'Is nervous but very well.' 12/3/16	

TABLE A (*continued*).

Case No.	Name.	Sex.	Age.	Physician or Surgeon and Date of First Attendance.	Systolic Blood Pressure.	Urine, S.G. and Albumin.	Duration of Symptoms.	Period under Observation.	Retinal Changes. Degree of Vascular Disease.	Evidence of Gross Cerebral Vascular Lesions.	Present Condition or Cause of Death.	Reference to Figs.
29	Henry N.	♂	65	Mr. Treacher Collins	218	1015 alb. 0			moderate	Has had a stroke	'Has been in Greenwich Infirmary with apoplexy.' 13/3/16	
30	Cornelius R.	♂	65	Mr. W. H. H. Jessop 27/12/15	195		$1\frac{1}{12}$	$\frac{6}{12}$	moderate	A mild stroke	'Is in good health but irritable,' 28/6/16. Dr. S. M. Lawrence	
31	George H.	♂	66	Mr. Holmes Spicer 4/4/11	165	1010 alb. + +	$4\frac{11}{12}$	$4\frac{11}{12}$	mild	none	Particularly robust. 18/3/16	
32	Robert C.	♂	66	Mr. Holmes Spicer 13/3/14	210	1019 alb. 0	$2\frac{1}{12}$	$2\frac{1}{12}$	moderate	A mild monoplegic attack	Has been better during the last 12 months than for a long time. 10/3/16	
33	Richard H.	♂	66	25/4/14	253	1016 alb. + 0	$2\frac{6}{12}$	2	severe	none	In very fair health, short of breath. 10/3/16	Fig. 14 Pl. 5
34	John P.	♂	78	Mr. Holmes Spicer 3/2/14	200	1016 alb. 0 0 0 0	5	$2\frac{1}{12}$	severe	none	'Father fairly well, sight poor, but he is 80.' 14/3/16	
35	Thomas C.	♂	80	Mr. Percy Flemming 8/6/13	150	1008 alb. + 0 0	$4\frac{9}{12}$	$2\frac{9}{12}$	mild	none	Looks very well, gets about well, and is now 83. 1/4/16	

TABLE B. CASES 36 TO 66.

Patients in whom Retinal Exudates were present in addition to Retinal Arterio-sclerosis, 'Arterio-sclerotic Retinitis'.

N.B. The observations with regard to the examinations of the urine, blood pressure, &c., at the head of Table A apply also to this Table.

Case No.	Name.	Sex.	Age.	Physician or Surgeon and Date of First Attendance.	Systolic Blood Pressure.	Urine, S.G. and Albumin.	Duration of Symptoms.	Period under Observation.	Retinal Changes	Evidence of Gross Cerebral Vascular Lesions.	Present Condition or Cause of Death.	Reference to Figs.
36	Jane B.	♀	45	6/6/13	245	1003 alb. +	$1\frac{1}{12}$	$\frac{5}{12}$	Many haemorrhages and dots of exudate. Arteries in places converted into white threads; l. disk atrophic	none	Died, Nov. 11, 1913. Cerebral haemorrhage. Dr. Kevern	
37	Kate G.	♀	49	Mr. Percy Flemming 30/1/14	215	1015 alb. + 0	$1\frac{9}{12}$	$1\frac{9}{12}$	Very marked irregularity of lumen of arteries. Many degenerative dots of exudate, quite small, forming a partial star figure	none? For 12 months the outer side of the left thigh and leg have felt as if they were in contact with a lump of ice, no warmth or wrapping makes any difference. Was awakened one night by a feeling of cold shooting up the back of the neck	Died, Nov. 6, 1914. 'Cerebellar cyst.' P. M.	

No.	Name	Sex	Age		B.P.	Urine			Ophthalmoscopic appearances	History	Result	Fig.
42	Harriet C.	♀	54	Mr. George Coats 14/12/12	220	1008 alb. +00+	3 3/12	3	Severe vascular disease. Degenerative dots in each eye; disk oedematous and later atrophic		Died, Dec. 6, 1915. 'Cerebral congestion with symptoms of effusion.' Dr. S. W. Davies	
43	Isabelle J.	♀	50	Mr. Holmes Spicer 15/4/13	290	1012 alb. +	1 6/12	1 1/12	Dots of exudate in form of a partial star in l. eye only. R. eye severe vascular disease	June, 1913. 'In Soho Sq. Hospital with a paralytic seizure'	Died, March, 1915. 'Cerebral thrombosis,' Dr. Gordon Donald	
44	John L.	♂	53	Mr. Devereux Marshall 3/2/14	210	1011 alb. +	1 6/12	1	A number of groups of degenerative dots arranged in relation with the veins	none	Died, Feb, 1915. 'Cardiac failure; a complication of diseases,' Dr. E. A. Ambrose	Fig.12
45	John P.	♂	53	Mr. Arnold Lawson 30/4/13	205	1012 alb. ++	1	1 6/12	Oedema of disk. Dots around macula in form of an irregular star		Died, Oct. 4, 1913. 'Had a stroke, lost all power of his left side, died within 24 hours'	
46	George H.	♂	60	Mr. A. C. Hudson 20/10/13	265	1005 alb. ++	10/12	10/12	Vascular disease severe, degenerative dots well marked	none	Died, Sept. 4, 1914. Cardiac failure. Dr. J. Hill	
47	James G.	♂	63	Mr. A. C. Hudson 6/3/13	235	1002 alb. +	1 1/2	1 1/12			Died, April 14, 1914. 'In a fit'	Fig. 3
48	Albert S.	♂	63	Dr. J. H. Drysdale		1016 alb. +			Marked irregularity of lumen of arteries. Partial star of dots in r. eye only		Died, Sept., 1915. 'Malignant growth of liver'	

F

TABLE B (*continued*).

Case No.	Name.	Sex.	Age.	Physician or Surgeon and Date of First Attendance.	Systolic Blood Pressure.	Urine, S. G. and Albumin.	Duration of Symptoms.	Period under Observation.	Retinal Changes.	Evidence of Gross Cerebral Vascular Lesions.	Present Condition or Cause of Death.	Reference to Figs.
49	William H. T.	♂	66	25/10/13		1013 alb. +	$2\frac{3}{12}$	$2\frac{1}{12}$	Severe vascular disease and scanty degenerative dots in r. eye L. disk pale	none	*Died*, Nov. 21, 1915. 'Chronic interstitial nephritis and uraemia.' Dr. May	
50	G. H. Q.	♂	67	Mr. J. H. Parsons 26/2/13	240	1016 alb. + + + + +	3	2	Well-marked vascular disease Rather copious exudate in form of a star in r. eye only		*Died*, Feb., 1915. 'In his sleep; cardiac failure.' Dr. J. A. Thornton	Fig. 13
51	Oliver R.	♂	71	Mr. J. H. Parsons 1/2/11	225	1013 alb. + +	$6\frac{5}{12}$	$4\frac{11}{12}$	Patches of exudate of 5 years' duration with vascular disease in both eyes	none	*Died*, Jan. 16, 1916. 'Cancer on the liver'	
52	Frederick B.	♂	65	Sir Wilmot Herringham 21/10/13	240	alb. +	2	$1\frac{2}{12}$	Severe vascular disease. A few degenerative dots in r. eye only		*Died*, Nov. 23, 1913. 'Cerebral haemorrhage.' Post-mortem. Dr. Hinds Howell	Figs. 15, 17, 20

No.	Name	Sex	Age	Referred by	B.P.	Urine			Condition of fundus	History	Result	Figs.
53	Augusta D.	♀	47	Mr. George Coats 24/5/13	180	1012 alb.00+0 0+00	$3\frac{4}{12}$	$3\frac{1}{12}$	Severe vascular disease. Arteries in places converted into white threads. Exudate in form of partial star of very fine texture in r. eye only	Oct. 18, 1913. Suddenly taken with shaking all down right side, right foot seemed to drag and have no use in it, all right leg numbed. Nov. 17, 1915, Twitchings all down right side	Works hard, looks and feels well. June 21, 1916	Fig. 9
54	Annie H.	♀	48	Mr. George Coats Mr. Gunn 28/11/08	215	1006 alb. 0 0 + +	$7\frac{7}{12}$	$7\frac{7}{12}$	Marked vascular disease upon which retinitis was engrafted later and persists now $5\frac{1}{2}$ years later	none	Not very well, but still attends as an out-patient. June 20, 1916	Figs. 10, 11
55	Ellen C.	♀	53	Mr. Worth 14/4/13	242	1008 alb. 0 + + 0	$3\frac{10}{12}$	3	Severe vascular disease, degenerative dots forming a partial star in l. eye only	'3 years ago sudden attack of numbness running up both legs; went off after three minutes'	Bad in health, heart very bad. Mar. 7, 1916	Fig. 4
56	Eliza E.	♀	55	Mr. Holmes Spicer 13/3/14		1009 alb. +	$1\frac{8}{12}$	$1\frac{8}{12}$	A good deal of exudate and vascular disease, irregular star arrangement		Is very well. Nov. 17, 1915	
57	Alice A.	♀	56	Mr. Holmes Spicer 16/9/13	235	1011 alb. + + +	$3\frac{3}{12}$	$2\frac{6}{12}$	Marked vascular disease, moderate amount of exudate with one or two soft-edged areas	'Numbness in legs and thighs as if half-dead'	'Mother very ill, dying, has not had a stroke.' Mar. 14, 1916	

F 2

TABLE B (*continued*).

Case No.	Name.	Sex.	Age.	Physician or Surgeon and Date of First Attendance.	Systolic Blood Pressure.	Urine, S.G. and Albumin.	Duration of Symptoms.	Period under Observation.	Retinal Changes.	Evidence of Gross Cerebral Vascular Lesions.	Present Condition or Cause of Death.	Reference to Figs.
58	Mary M.	♀	60	3/6/13	160	1011 alb. 0 0 0	$2\frac{9}{12}$	$2\frac{9}{12}$	Large haemorrhage of heterogeneous texture, a little exudate and moderate vascular disease in l. eye only; r. eye mild vascular disease only		'My health is better, my eye does not trouble me.' Mar. 15, 1916	Fig. 8
59	Eliza P.	♀	60	Mr. Percy Flemming 14/2/13	223	1012 alb. + + 0 0	$3\frac{1}{12}$	3	Moderate vascular disease with scanty exudate which completely disappeared	none	Thoroughly fit in every way. Feb. 28, 1916	
60	Jane B.	♀	65	Mr. Percy Flemming 10/5/13	300	1008 alb. + + +	$3\frac{6}{12}$	3	Extreme vascular disease with a little exudate in l. eye only	Feb. 1914. Had a stroke, from which she has a good deal recovered	Is in Hackney Infirmary, nearly blind, retinal arteries largely converted into fibrous-looking threads. Blood pressure, 290 mm. Is not bed-ridden. June 2, 1916	
61	Louisa S.	♀	65	Mr. Percy Flemming 30/5/13	197	1010 alb. + 0 0 0	$2\frac{4}{12}$	$2\frac{10}{12}$	Severe vascular disease with a little exudate in r. eye only	Gives a good account of a mild stroke in 1910 and a second in 1911	Still attends as an out-patient, no fresh stroke. Mr. Percy Flemming, June 4, 1916	

No.	Name	Sex	Age	Date / Observer							Remarks
62	Eliza B.	♀	67	1/10/13	210	1012 alb. 00	$2\frac{9}{12}$	$2\frac{5}{12}$	Severe vascular disease, one large haemorrhage, and a little exudate in one eye only	none	'Am very well in health and my eye improves', Mar. 15, 1916
63	Abraham B.	♂	66	Mr. Holmes Spicer 20/5/13	175	1010 alb. +++	$3\frac{5}{12}$	$2\frac{1}{12}$	Severe vascular disease with dots of exudate and one or two soft-edged areas in r. eye only	none	'Still active and able to take walking exercise and can read,' Mar. 5, 1916
64	William T.	♂	63	Mr. Treacher Collins 30/12/12	220	1009 alb. ++++	$2\frac{8}{12}$	$1\frac{3}{12}$	Severe vascular disease with well-marked exudate which largely disappeared under observation	none	'Can walk 3 or 4 miles at a good pace,' Apr. 2, 1914
65	Charles L.	♂	55	Mr. George Coats	175	1015 alb. 0	$3\frac{7}{12}$	$3\frac{7}{12}$	Moderate vascular disease. A few degenerative dots in each eye which completely disappeared		Is in very good health. July 1, 1916
66	Sophie R.	♀	65		205	1010 alb. +			One or two small areas of exudate in each eye		Not traced. 'Death certificate has not been issued.' *Registrar General*, June 30, 1916

ANALYSIS OF PATIENTS IN TABLE A

i. e. those in whom Retinal Arterio-sclerosis alone was present.

Age.
    Average age of 17 females . . . . 57 years
        ,,   ,,   18 males . . . . 61 ,,

Systolic Blood Pressure.
    Average of 16 females . . . . 216 mm. Hg
    ,,   ,,   14 males . . . . 204 ,,   ,,

Degree of Vascular Disease.
    Females.   Mild 2
                Moderate 5
                Severe or very severe 10
    Males.   Mild 3
                Moderate 8
                Severe or very severe 7

Present Condition.
    Females.   4 are known to have died, 2 of them of cerebral haemorrhage.
                10 are known to be alive 4½ years on an average since the onset of symptoms, 6 of whom are in reasonable health, i. e. able to be about their usual occupations.
                3 are untraced.
    Males.   6 are known to have died, 1 of them of cerebral haemorrhage.
                9 are known to be alive on an average of 3 years after the onset of symptoms, 6 of whom are in reasonable health.
                3 are untraced.

Evidence of Gross Cerebral Vascular Lesions.
    Females.   Definite evidence present in 5, absent in 9.
    Males.   ,,   ,,   ,,   6   ,,   6.

ANALYSIS OF PATIENTS IN TABLE B

i. e. those in whom Arterio-sclerotic Retinitis was present.

Age.
    Average age of 19 females . . . . 58 years
        ,,   ,,   12 males . . . . 62 ,,

Systolic Blood Pressure.
    Average of 18 females . . . . 224 mm. Hg
    ,,   ,,   10 males . . . . 219 ,,   ,,

Degree of Vascular Disease.
    Females.   Moderate 3
                Severe 11
                Very severe 4
    Males.   Moderate 2
                Severe 9
                Very severe 1

Present Condition.
    Females.   8 are known to have died, 5 certainly of cerebral haemorrhage or thrombosis.
                11 are known to be alive 3 years and 5 months on an average after the onset of symptoms, of whom 6 are in reasonable health.
                1 is untraced.
    Males.   9 are known to have died, 2 certainly of cerebral haemorrhage (Case 45 and 52 : Case 47 ?).
                3 are known to be alive and in reasonable health 2 years 10 months after the onset of symptoms.
                0 are untraced.

Evidence of Gross Cerebral Vascular Lesions.
    Females.   Definite evidence present in 8, absent in 4.   (Cases 37, 40, 55, and 57 are considered doubtful and are not included.)
    Males.   Definite evidence present in 3, absent in 6.

TABLE C.

Patients in whom Sudden Thrombosis of the Retinal Artery has occurred.

For particulars as to evidence of gross cerebral vascular lesions, present condition, &c., see Tables A and B.

Name and Age.	Average Systolic Blood Pressure.	History.	Condition of Affected Eye.	Condition of Other Eye.
Michael L. 53 (Table A. 6)	230	10 days ago suddenly went blind in r. eye whilst out walking	Arteries exceedingly small. Disk a little pale. There is still the remains of the cherry red spot at the macula with surrounding coagulation necrosis. V = Hand movements	Arteries very bright. Field complete. V = $\frac{6}{6}$
Arthur R. 55 (Table A. 16)	205	Went to bed at 8 o'clock quite well. Awoke at 10 o'clock and found himself blind in the r. eye. 19/3/13	Arteries show marked irregularity of lumen. Veins severely cut into. Disk very pale. Cherry spot at macula. V = Hand movements in certain positions	Moderate arterio-sclerosis. V = $\frac{6}{6}$
Sarah S. 43 (Table A. 11)	270	Woke up 6 weeks ago and found she was blind. L. eye was previously blind. March 9, 1915	Very severe disease of arteries which are very fine. No cherry red spot. V = Hand movements	V = Hand movements
Walter W. 66 (Table A. 8)	250	6 months ago awoke in the night and found he couldn't see with r. eye. April 2, 1914	Disk very pale. Arteries on disk very small. Marked evidence of sclerosis	Moderate arterial disease. V = $\frac{6}{6}$
William H. T. 66 (Table B. 49)		Quite sudden blindness in l. eye one morning. Oct. 10, 1913 (branch only involved)	Disk pale	V = $\frac{6}{9}$ Later became involved

TABLE C (*continued*).

Name and Age.	Average Systolic Blood Pressure.	History.	Condition of Affected Eye.	Condition of Other Eye.
Martha L. 60 (Table A. 23)	250	Awoke in morning 3 days ago and found she couldn't see with the l. eye. No improvement since. June 21, 1913	Typical cherry red spot at macula and coagulation necrosis. (72 hours after onset) Perception of light only	Severe arterial disease. $V = \frac{6}{8}$
Louisa M. 64 (Table A. 3)		2 weeks ago there was a flash before the r. eye and she has not seen with it since. April 9, 1907	Arteries very small and in places converted into white lines. Retina very oedematous in region of macula. $V =$ Hand movements	$V = \frac{6}{60}$
Cornelius R. 65 (Table A. 30)	195	Woke up on Dec. 27, 1915, and found himself blind in l. eye	Coagulation necrosis over central regions of fundus. No cherry red spot. Arteries but little if at all reduced. ? Thrombosis of a ciliary artery	Blind from an old nebula
Louis C. 80	170	When coming out of a shop on Oct. 30, 1915, he suddenly noticed he was blind in the l. eye	He has the cherry red spot at the macula and surrounding coagulation necrosis. (48 hours after onset) $V = \frac{2}{60}$	He gets attacks of blindness of about 5 minutes' duration in this eye. $V = \frac{6}{12}$

TABLE D.

Showing the condition of the Retinal Arteries as regards the Ophthalmoscopic Evidence of Sclerosis in 44 Patients admitted to St. Bartholomew's Hospital suffering from a Gross Cerebral Vascular Lesion.

The condition of the arteries is indicated by 'nat.' = natural, through $\frac{+}{2}$, +, to + +, the last indicating that severe or very severe disease was present. The arrangement is in the order of increasing blood pressure.

Case No.	Name.	Sex.	Age.	Date of Admission.	Under the care of.	Systolic Blood Pressure.	Condition of Retinal Arteries.	Presence of Retinal Exudates.	Urine, S. G. and Albumin.		Diagnosis.
1	F. N.	♂	62	25/2/15	Dr. Langdon Brown	110	+	0			Cerebral thrombosis
2	T. C.	♂	47	8/2/16	Dr. A. E. Garrod	120	nat.	0	1027	0	Hemiplegia
3	W. S.	♂	53	22/2/14	,,	138	,,	0			Cerebral thrombosis
4	A. N. O.	♂	60	10/11/14	Sir W. Herringham	140	,,	0	1015	0	,, ,,
5	M. B.	♀	65	24/8/13	Dr. Howard Tooth	140	$\frac{+}{2}$	0		haze	,, ,,
6	W. S.	♂	74	27/3/14	Sir W. Herringham	150	+	0	1011	haze	,, ,,
7	F. T.	♂	60	18/8/15	,,	150	$\frac{+}{2}$	0	1017	0	,, ,
8	H. S.	♂	65	9/11/13	,,	157	nat.	0	1020	0	,, haemorrhage
9	J. M.	♂	44	4/1/16	Dr. Morley Fletcher	160	+ +	0			,, thrombosis
10	D. T.	♂	72	27/1/14	Dr. Garrod	165	$\frac{+}{2}$	0	1005	0	Aphasia
11	J. R.	♂	39	5/9/14	Dr. Tooth	185	+ + oedema of disk	$\frac{+}{2}$	1008	haze	Cerebral thrombosis
12	J. E.	♂	63	20/4/13	Dr. Morley Fletcher	190	nat.	0	1020	0	,, ,, P.M.
13	J. F.	♂	71	6/11/13	Dr. Thursfield	190	$\frac{+}{2}$	0			,, ,,
14	L. D.	♀	54	29/8/14	Dr. Morley Fletcher	190	+ +	0	1010	0	Right hemiplegia
15	W. J.	♂	53		Dr Horder	194	+ +	0	1018	trace	Cerebral haemorrhage
16	M. F.	♀	51	17/10/13	Dr. J. Calvert	200	+ +	0	1009	cloud	,, thrombosis
17	E. H.	♀	43	20/5/13	Dr. Tooth	215	+ +	0		cloud	,, haemorrhage. P.M.
18	M. B.	♀	59	25/2/16	Dr. Morley Fletcher	218	+	0			Hemiplegia
19	A. S.	♂	61	25/10/14	Dr. H. S. Hartley	220	+ +	+		haze	Cerebral haemorrhage

TABLE D (*continued*).

Case No.	Name	Sex	Age	Date of Admission	Under the care of	Systolic Blood Pressure	Condition of Retinal Arteries	Presence of Retinal Exudates	Urine, S.G. and Albumin	Diagnosis
20	W. P.	♂	46	25/1/16	Dr. Tooth	225	nat. ?	0		Hemiplegia
21	H. T.	♂	65	3/2/15	Dr. Morley Fletcher	225	+	0	1018 trace	Cerebral haemorrhage P.M.
22	H. T.	♀	63	23/12/14	Dr. Garrod	228	oedema of disk ±/2	0	1005 trace	,, ,, ¹ P.M.
23	E. S.	♀	37	6/4/14	Sir W. Herringham	230	++	+		,, thrombosis
24	G. A.	♂	56	13/6/16	Dr. Tooth	235	++	0	1018 trace	Hemiplegia
25	J. G. G.	♂	62	22/2/14	Sir W. Herringham	238	++	0		Cerebral haemorrhage
26	W. B.	♂	65	21/10/14	,,	240	++	+	cloud	,, ,, P.M.
27	A. W.	♂	52	15/1/16	Dr. Garrod	240	++	+	1018 cloud	,, ,,
28	T. S.	♂		5/3/16	,,	240	++	+	cloud	,, thrombosis P.M.
29	S. P.	♂	59	5/12/13	Sir W. Herringham	248	±/2	0		,, haemorrhage
30	E. G.	♂	30	13/10/13	Dr. Garrod	250	+	+	1016 0	,, ,,
31	M. L.	♀	44	21/11/13	Dr. Morley Fletcher		++ disks pale	0		,, thrombosis
32	F. R.	♂	47	14/4/14	Sir W. Herringham		++	0		,, haemorrhage
33	C. A.	♀	48	31/10/13	Dr. James Calvert		nat.	0	1015 0	,, thrombosis
34	T. H.	♂	53	7/10/15	Dr. Morley Fletcher		,,	0		,, ,,
35	E. S.	♀	57	17/5/15	Dr. Calvert		++	+	trace	,, ,,
36	R. S.	♀	58	6/12/15	Dr. J. H. Drysdale		+	0		,, ,,
37	W. P.	♂	60	16/1/14	Sir W. Herringham		nat.	0		,, ,,
38	G. B.	♂	60				,,	0		,, ,,
39	K. P.	♀	62	13/10/14	Dr. Drysdale		++	0		,, haemorrhage
40	T. W.	♀	63	,,	,,		++	0		Hemiplegia
41	H. Y.	♀	63	17/1/14	Sir W. Herringham		nat.	0		Cerebral haemorrhage P.M.
42	T. G.	♀	68	10/10/14	Dr. Garrod		+	0	1015 0	,, thrombosis
43	E. E.	♀	79	31/10/13	Dr. Tooth		++	0	1020 trace	,, ,, P.M.
44	H. I.	♂	44	28/3/13	Dr. Drysdale		nat.	0		,, ,,

¹ See Figs. 16, 18, and 19.

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DESCRIPTION OF FIGURES.

PLATE 2, FIG. 1.   Case 22, Table A.   Shows very great variability of lumen of the arteries.   The drawing was made on Sept. 13, 1913, and on March 4, 1916 ($2\frac{1}{2}$ years later), the condition was quite unchanged; the individual constrictions could be identified and were unaltered.   See chart of visual field corresponding, Chart 2.

FIG. 2.   Case 40, Table B.   Shows great variability of lumen of the arteries, and two groups of degenerative dots.   The drawing was made Aug. 14, 1913.   The patient died 'in uraemia' Feb. 17, 1914.

FIG. 3.   Case 47, Table B.   Shows variability of lumen of the arteries, oedema of the disk, and a group of degenerative dots.   The drawing was made July 3, 1913.   The patient died 'in a fit' April 14, 1914.

FIG. 4.   Case 55, Table B.   Shows variability of lumen of the arteries, the veins are severely cut into, and groups of degenerative dots are seen ranged around the small veins.   The drawing was made on April 14, 1913, and on May 20, 1916, the constrictions of the arteries were quite unchanged and the dots had completely disappeared, leaving no trace behind.

PLATE 3, FIG. 5.   Case 21, Table A.   Shows a single gross haemorrhage of heterogeneous texture probably infiltrating most of the layers of the retina.   The first drawing was made on Jan. 16, 1914, and on March 4, 1916, all signs of the haemorrhage had completely gone and an artery and vein were seen crossing the area.   There was nothing to indicate with certainty the source of the blood, but the artery was very bright and showed marked variability of calibre.

FIG. 6.   The above composite drawing is to indicate the length of time which is necessary for the disappearance of different types of retinal haemorrhages.   The drawings of the individual haemorrhages have been taken from their proper notes and have been brought together here.   An attempt has been made to represent as nearly as possible the size, shape, position, texture, and density of the haemorrhages.   The length of time which elapsed between *their discovery* and their complete *disappearance* is given.

1. Table B, Case 42: disappeared in . . . . . . 2 months.
2. ,, ,, ,, 64: slight traces present after . . . . 3 ,,
3. ,, ,, ,, 60: disappeared in . . . . . . $3\frac{1}{2}$,,
4. ,, ,, ,, 58: the area was still mottled with blood after . 4 ,,
5. ,, A, ,, 35: this small area and this area only was still the site of small haemorrhage after . . 2 years 10 months.
6. ,, B, ,, 62: disappeared in . . . . . . 7 weeks.
7. From a case of renal retinitis: disappeared in . . . . 30 days.
8. Table B, Case 61 : disappeared in . . . . . . 8 weeks.

FIG. 7.   Case 8, Table A.   Shows extreme reduction of lumen of the arteries, with thickening of the arterial walls, in a case in which thrombosis of the artery occurred.

PLATE 4, FIG. 8.   Case 59, Table B.   Shows the relation of the degenerative dots to the radicles of the small veins; every individual dot that could be seen was incorporated in the drawing.   The drawing was made on Dec. 23, 1913, and on Feb. 28, 1916, all the dots had completely disappeared and left no trace behind them.

FIG. 9.   Case 53, Table B.   Shows variability of calibre of the arteries, and a group of degenerative dots in the form of a partial macular star.   A small patch of pipe-stem sheathing is seen on the lower temporal artery.   The drawing was made on June 28, 1913.   On Feb. 14, 1914, the star had gone except for one or two minute dots, and the pipe-stem sheathing and the small haemorrhage on the vessel below had completely disappeared.   June 20, 1916: There is no trace of any of the above changes to be seen and no fresh changes have developed.   The branch *a* is now a white fibrous-looking thread.

FIG. 10.   Case 54, Table B.   Shows some of the changes in the retina in a patient who had had arterio-sclerotic retinitis for more than five years.   The veins are cut into by the arteries, and there are degenerative dots ranged around the veins and larger areas of exudate.

FIG. 11.   Case 54, Table B.   To show the arrangement of the degenerative dots around venous radicles.

Fig. 12.   Case 44, Table B.   As in Figs. 8, 11.

Fig. 13.   Case 50, Table B.   Plaque-like or pipe-stem sheathing of an artery which completely disappeared under observation and left no trace.

Fig. 14.   Case 33, Table A.   Arterio-venous crossing.   A drawing of this crossing was made on April 28, 1914 (Head).   The above was made on March 10, 1916.   No discoverable alteration had occurred in the course of two years.

Plate 5.   Case 33, Table A.   Shows great reduction in calibre of the lower arteries with partial optic atrophy.   Great displacement of the line of the upper temporal vein is seen where it is crossed by the corresponding artery (April 28, 1914).   This crossing was quite unaltered on March 10, 1916.   See Fig. 14.

Plate 6.   Case 59, Table B.   Shows degenerative dots in the immediate territory of the small venous radicles (Dec. 23, 1913).   All of these had disappeared and left no trace behind on Feb. 28, 1916.

Plate 7.   Case 60, Table B.   Shows bright arteries which are also somewhat tortuous. In one place a small artery is converted into a fibrous-looking thread.   A number of very fine degenerative dots are present.   The veins are engorged, tortuous, and severely cut into and displaced where they are crossed by the arteries.   At one place just below the disk a vein is seen riding over a small artery (Jan. 24, 1914).   On June 2, 1916, the changes were similar in kind but advanced in degree; the arteries were in large part converted into white fibrous-looking threads.

Plate 8, Fig. 15.   Case 52, Table B.   Section of a retinal artery which during life was exceedingly bright and burnished (silver wire) in appearance.

Fig. 16.   Case 28, Table D.   Shows the condition of the choroidal arteries; a few red blood cells are present in the greatly constricted lumen.   The choroidal vessels were noted during life to show signs of severe sclerosis.   See Figs. 18 and 19.

Fig. 17.   Case 52, Table B.   Section through branches of the lenticulo-striate arteries of a man who died of cerebral haemorrhage.   For retinal arteries of same case see Fig. 15.

Fig. 18.   Case 28, Table D.   Stained with orcein.   Shows four roughly circular collections of hyaline exudate in the internuclear layer which gave rise to the appearance of the degenerative dots of arterio-sclerotic retinitis.   See p. 43, Figs. 16 and 19.

Plate 9, Fig. 19.   Case 28, Table D.   From a case of arterio-sclerotic retinitis.   Shows the conversion of the nerve fibre layer into a sponge-like network.   Seen ophthalmoscopically the area had soft edges, was of a dirty white colour, and the retinal vessels (see right-hand edge) ran unobscured over it.   See also Figs. 16 and 18.

Fig. 20.   Case 52, Table B.   Shows gangliform degeneration of the nerve fibre layer. See also Figs. 15 and 17.

Fig. 21.   Section through the retina of a woman who died of nephritis, in whom well-marked renal retinitis with a macular star was present.   Treated with Flemming's solution and picrocarmine.   Shows numerous large phagocytic cells crowded with fat in the outer layers of the retina; many of these cells are in close relation with the external limiting membrane.   The nerve fibre layer is just out of the section above.
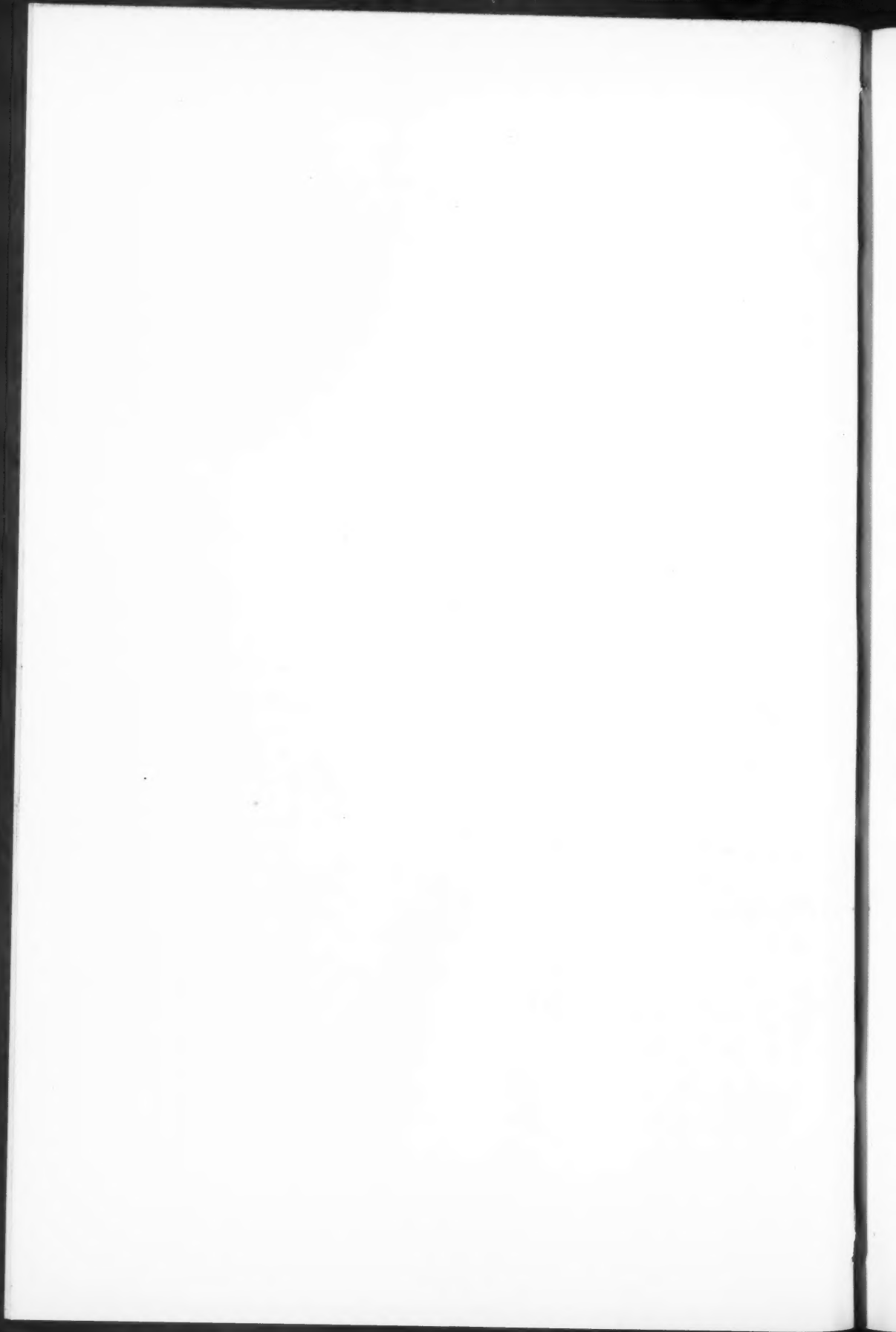
Fig.1

Fig.2
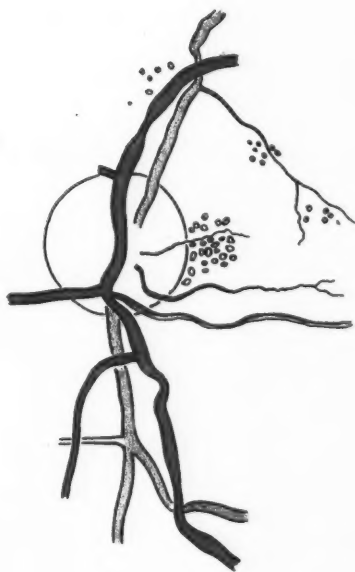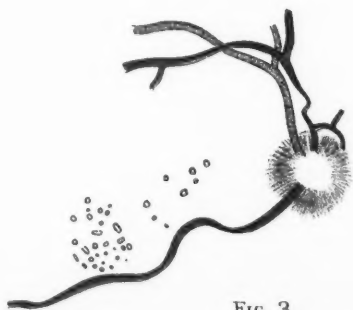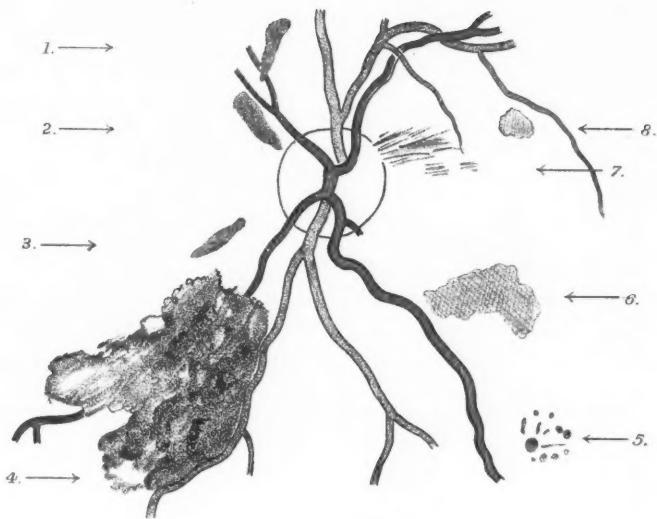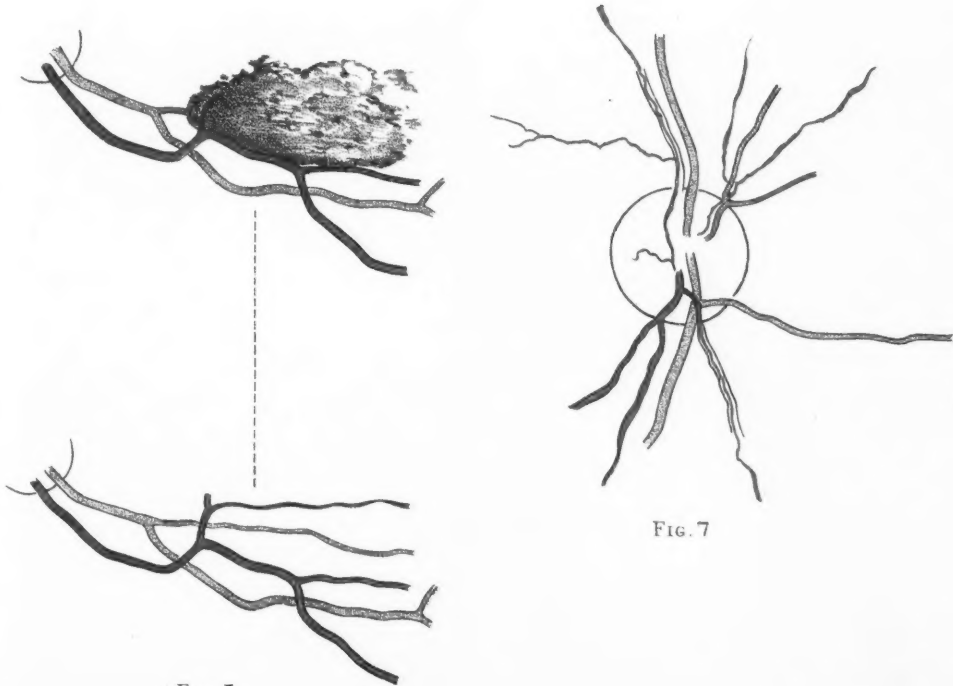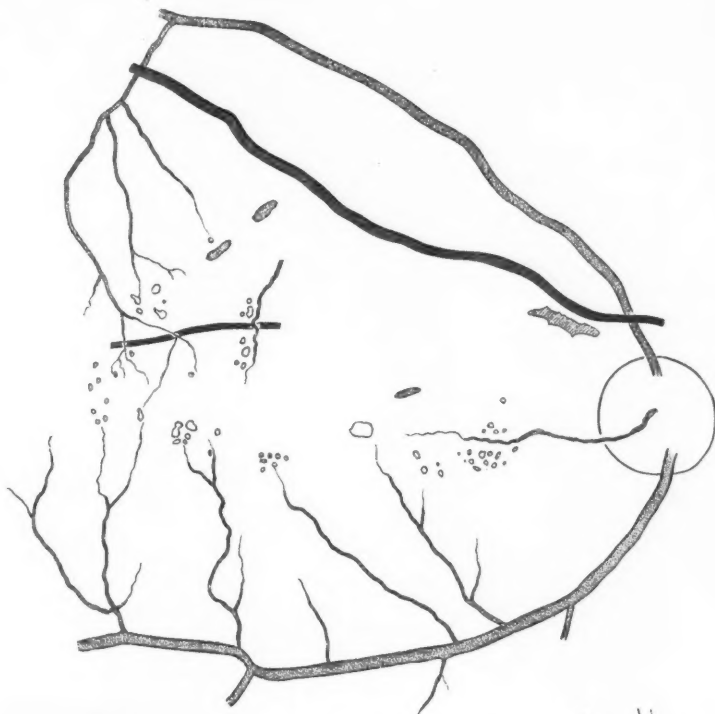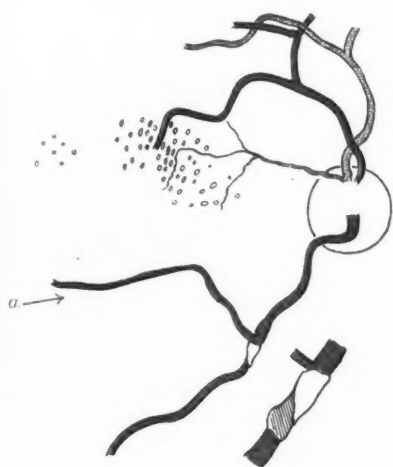
Fig.3

Fig.4

Fig. 6

Fig. 5

Fig. 7

FIG. 8

FIG. 9
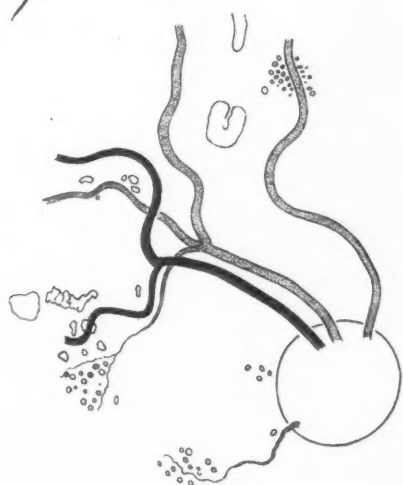
FIG. 10

FIG. 13

FIG. 11.

FIG. 14

FIG. 12

Qu
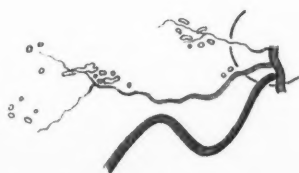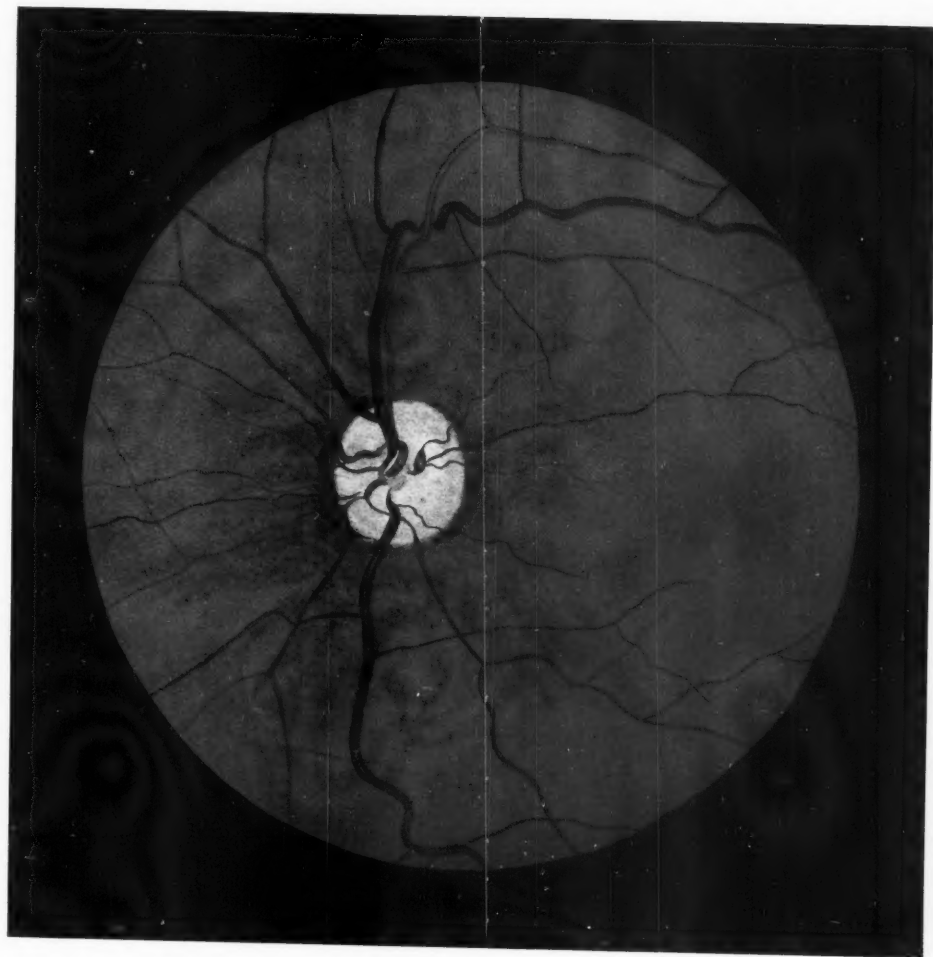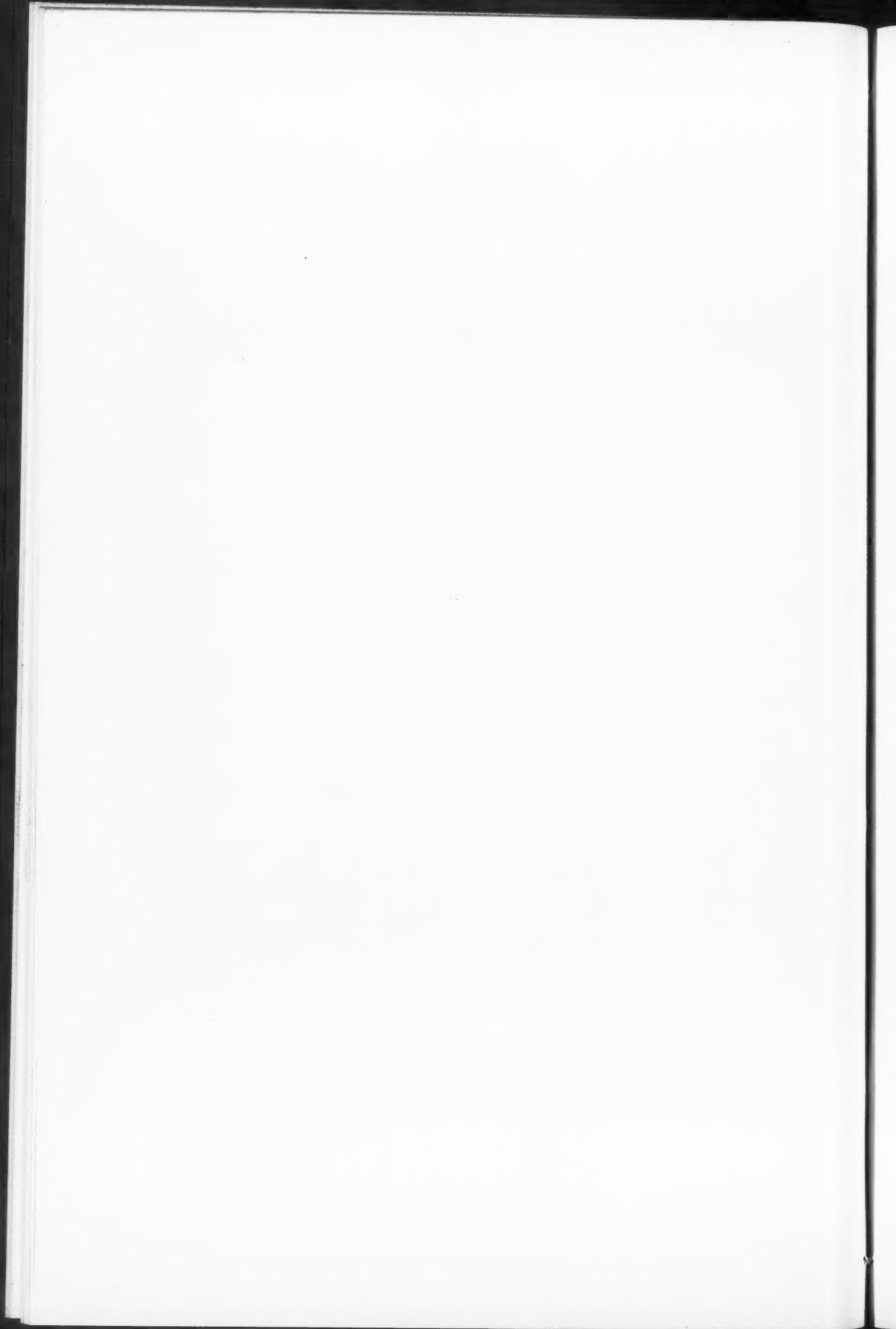
AW HEAD 1916

FIG. 17
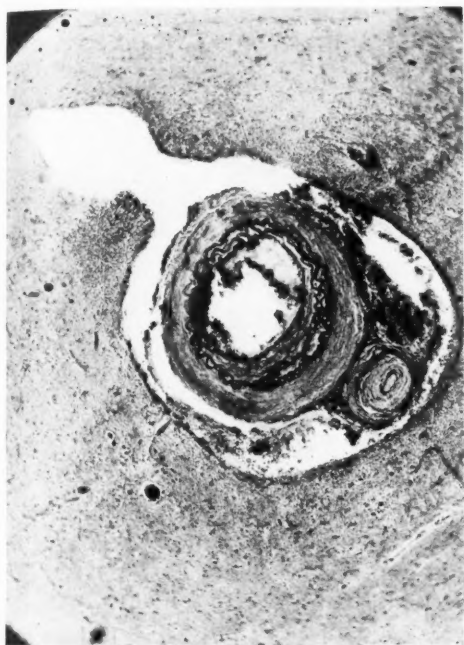
FIG. 18
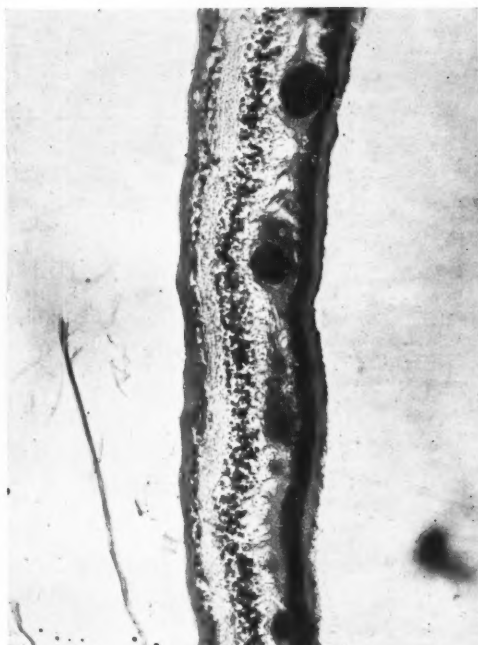
FIG. 15
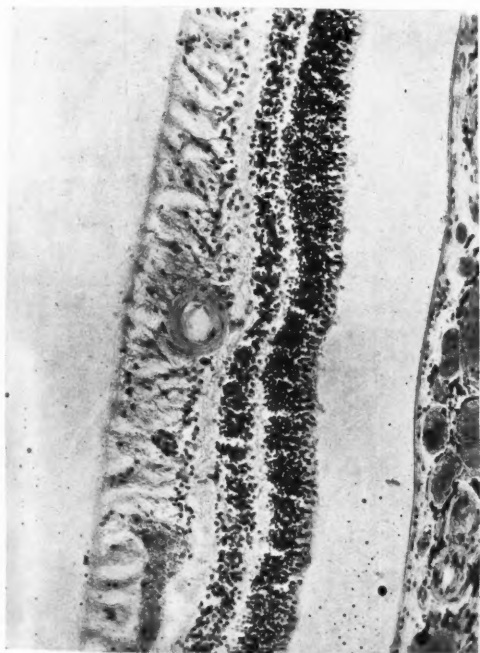
FIG. 16
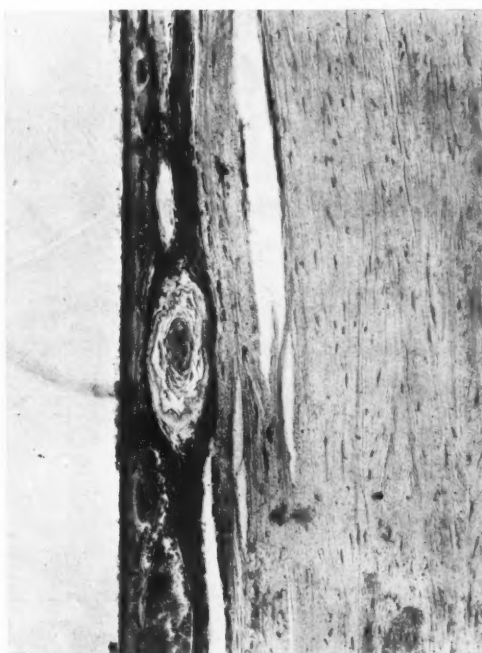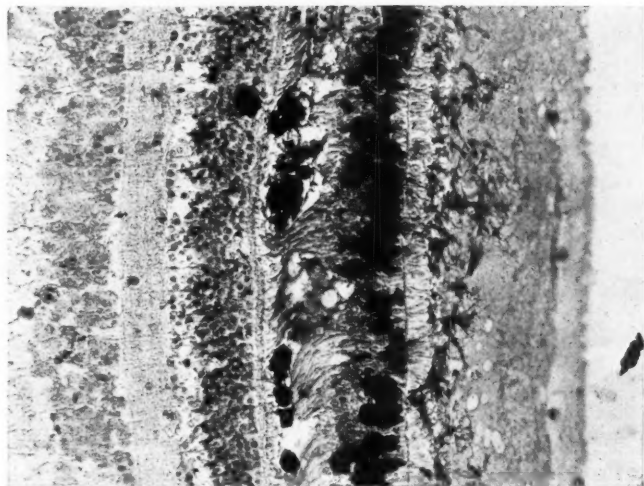
Fig. 21

Fig. 19

Fig. 20

ON THE EARLY STAGE OF WOUNDS OF THE CHEST

By W. P. HERRINGHAM

I HAVE lately had the opportunity, owing to the kindness of Lieut.-Colonel R. J. C. Thompson, of staying at a casualty clearing station near the front and observing daily the patients with wounds of the chest.

It will be of use to add this study of the early stages of chest wounds to the admirable reports of my colleagues at the base who have seen them later on. But mine is necessarily much less perfect. It is impossible to examine such cases elaborately when they are but recently brought in. Often it is not till the third day that the back can be percussed and ausculted.[1] Our nursing personnel is much smaller than at the base.

When patients are first admitted they are often collapsed from the effects of the drive down. Ambulances are driven with great consideration for patients. I have often watched and admired the driving. But nothing can avert the jolting of a bad road, and no roads at the front are other than very bad. It is common to be unable to feel, and not uncommon to be unable even to hear, the heart on the day of admission, which is usually the day after the wound. It has been impalpable in fifteen cases on the third day, in seven cases on the fourth day, and in one case, which lay out three days before being brought in, on the fifth day after the wound. Respiration is often very shallow, partly from collapse and partly from the pain which it causes. It is difficult then to say how much this weakness of breathing is due to injury of the lung.

Luckily most wounded men sleep easily. In cases of distress or restlessness, morphia is very beneficial. I never saw it do any harm and I use it very freely. By the next day they are usually comparatively comfortable.

Unless a case shows symptoms of sepsis, or has some complication which renders it more severe than the ordinary, my rule, which was begotten of necessity but adopted of choice, has been to evacuate when seventy-two hours have been completed from the time that the wound was received. Bradford's statistics show that after this there is practically no risk of haemorrhage, and

[1] In my case notes 'side' means the axillary surface. I divide the thorax into right and left front, side, and back.

I do not see any reason to expect that early evacuation would increase the danger of septic infection. I asked Colonel Kingston Fowler at the base, and Lieut.-Colonel Meadows at the stationary hospital on the way thither, to let me know at once if they saw any bad results from my practice, and have been reassured by them. It is much better for patients to go to the base if they are going to be septic, as they can be better treated there. In only a few cases did the symptoms of infection appear so early that I retained the patients.

General statistics, such as the proportion of shrapnel to bullet wounds, and the common site of wounds, can be obtained better from the base. It is perhaps superfluous to say that a bullet that goes right through the chest is by far the most favourable. With bits of shell or shrapnel an exit wound is much less common, and there is no limit to the vagaries of their course. They furnish the greater number of deaths.

Of 211 consecutive cases twenty-two died at the clearing station and the remainder were evacuated to the base. The twenty-two deaths were as follows : Three were due to septic infection of the external wounds by gas-forming organisms. The condition of the lungs was not unfavourable. Two were complicated by spinal injuries which caused paralysis and death within a few days.

Five were complicated by severe abdominal injuries sufficient in themselves to cause death. In one the entire stomach had been dragged into the pleural cavity. The man was too ill to examine and I cannot therefore describe the physical signs. In two others the spleen was torn right across, yet there was little haemorrhage. In one of these cases the patient lived eight days. One case was apparently dying from abdominal injury, though shot in the chest also. Two cases died from lesions of the heart.

Case I.   Pte. Ad.   *Wound of heart.*
Hit July 19. Shrapnel wound 1″ above and 1″ inside l. nipple ; no exit. Haemoptysis.

July 20. Heart's apex 1½″ outside nipple, l. sounds natural. P. 136. R.48. Lungs : l. front and side, breath sounds well heard ; r. front and side, breath sounds audible but weak.

July 21. Heart as yesterday. P. 152. R. 44. Surgical emphysema r. front.

July 22. Lungs : l. front, rhonchus ; r. front, râles in upper part, loud and consonating below nipple ; both dull behind with râles ; much distress. Death.

Wound perforated thorax at inner margin of l. fifth space. On removing sternum a large mass of clot in front of pericardium, which latter projected 1½″ beyond r. border of sternum. The clot covered a wound which went through not only the pericardium but also the anterior wall of the r. ventricle, admitting a finger. Pericardium contained blood clot and was adherent by this to the heart all over. Back wall of ventricle uninjured. Rest of heart natural. (The missile had scraped a hole in passing across the front of the heart.) Both lungs much congested. L. pleura contained much blood. L. lung partially collapsed. Missile not found.

This man had lived three days with a hole in his r. ventricle.

Case II.   Pte. Cle.   *Pericarditis from bullet.*

Hit July 10.   Bullet wound of l. back ; no exit.   Haemoptysis.

July 11.   Heart extended to r. nipple line ; sounds natural.   P. 120.   R. 40. Lungs : r. natural ; l. tympanitic in front ; breath sounds weak.

July 12.   Heart to $2\frac{1}{2}''$ r. of mid-line.   Pericardial friction.   P. 120.   R. 36 Lungs : both fronts resonant ; loud rhonchus on r. ; l. little movement and very little breath sound.   Great expiratory dyspnoea.   Death.

L. pleura nearly full of bloody liquid with clots.   L. lung collapsed and covered with lymph.   Heart displaced to r.   Pericardium contained a few ounces of turbid fluid.   Heart covered with lymph but uninjured.   Bullet lying in back of pericardium.   R. lung natural.

Nine cases died from pulmonary lesions.

Case III.   Pte. Lu.   A great hole had been torn in the l. back.   The lung was entirely collapsed.   He lived five days.   No autopsy was made.

Case IV.   Sgt. Ma.   *Death by external haemorrhage from lung.*

Hit July 16.   Bullet : (*a*) entry, r. scapula ; (*b*) exit, r. edge of sternum, second space.   Haemoptysis.

July 17.   Heart's apex indefinite.   P. 96.   R. 24.   Wound in lung bleeding much ; plugged.

July 18.   P. 96.   R. 30.   Lungs : l. front and back natural save a little sibilus ; r. front covered with dressing ; back impaired and silent.   Vomited after all food.

July 20.   Wound looking well, though very deep ; much purulent discharge.

July 21.   Two more severe haemorrhages from front wound, in spite of plug. Death.

A large hole right through the r. lung.   The lung was universally adherent and had not collapsed.   Aorta, vena cava, pericardium, and heart all uninjured. L. lung natural.

The want of collapse had no doubt kept the wound, which was a large cavity, open and allowed the haemorrhages to recur.   The adhesions were soft and, I think, subsequent to the wound.   Collapse is the natural protection against haemorrhage.

Case V.   Pte. Ri.   *Large haemothorax.*   *Congestion of opposite lung.*

Hit July 12.   Shrapnel ; behind r. shoulder ; no exit.

July 13.   Heart's apex natural.   P. 132.   R. 28.   No fever.   Vomiting all food.   Delirious at night.

July 14.   Lungs : l. rhonchus, otherwise natural ; r. lung emphysematous in front, impaired in axilla ; breath sounds a little weaker than l.   Death.

Heart natural ; very little displaced.   A little extra fluid in pericardium. A large amount of blood in r. pleura.   R. lung partly carnified, wound in upper lobe.   L. pleura empty.   L. lower lobe deeply congested, hardly any air in it.   L. upper lobe partly collapsed.   Some air escaped from l. pleura on opening, but no wound traced in lung.   Abdomen natural.

Case VI.   Sapper Le.   *Large haemothorax with some air.*   *Collapse of opposite lung.*

Hit July 14.   Shrapnel.   Multiple.   Haemoptysis.

July 15.   Heart's apex $1\frac{1}{2}''$ outside nipple line, fourth space.   P. 140.   R. 48. Lungs : l. loud rhonchi front and side ; r. breath sounds faintly audible in front. Great tenderness lower front and side.

July 16.   Died.

R. pleura contained some air, but was almost choke-full of blood ; r. lung collapsed and almost airless, floating on surface. Heart entirely to l. of mid-line, otherwise natural. L. pleura natural. L. upper lobe natural ; lower lobe largely collapsed. Only the front part contained air. Probably the collapse occurred during the last twenty-four hours.

Case VII. Corp. Cla. *Congestion of whole of r. and lower lobe of l. lung.*

Admitted too ill to question. Died same day.

Wound behind r. shoulder and in r. upper lobe. Whole of r. lung was solid with congestion. Petechiae on surface. L. lower lobe in same condition, upper lobe natural. No wound in l. lung ; no fluid in either pleura. Heart and abdomen natural.

Case VIII. Lt. C. *Pneumothorax.*

Hit July 30. Shrapnel ; r. scapula. Could not be fetched in for twenty-four hours. Haemoptysis.

Aug. 2. Heart's apex impalpable. P. 100. R. 24. T. 101°. Lungs : l. apex expanding well ; r. not moving, silent.

Aug. 3. Heart's apex in sixth space anterior axillary line ; sounds natural. P. 96. R. 28.

Aug. 4. Pulse rapid and weak ; r. side aspirated. A considerable amount of air removed.

Aug. 5. Heart's apex has not altered, but the patient is more comfortable.

Aug. 7. Again very short of breath. Heart's apex in mid axillary line. Aspirated again. A little blood-stained fluid and a great deal of air. Both quite sweet.

Aug. 8. A little better, but again became very restless.

Aug. 9. Death.

Temperature was high throughout.

Air escaped from r. pleura at great pressure on opening. R. lung collapsed to a thin layer entirely concealed by lymph. Pleura contained about two pints of thin blood-stained fluid. Mediastinum forced over to l. of sternum. Ht. and pericardium natural. L. pleura and lung natural.

In this case the air in the pleura certainly did not come from the lung. It may have been formed by organisms, but there was no smell as is in such cases usual. It may have been sucked in through the wound by the movements of the chest.

Case IX. Pte. Cu. *Pneumothorax. Congestion of opposite lung.*

The wound, which was in the lower part of the r. back, allowed free air entry. It had been enlarged and a tube put through it into thorax. For the first three days he did well. On the fourth day the breath sounds in the l. lung were natural, but the temperature rose to 102·8°. On the fifth day he was much distressed and died that night.

Heart entirely to l. of mid-line. Pericardium and heart natural. R. lung collapsed and lying against spine. No fluid in pleura ; no smell. L. pleura natural. L. upper lobe natural ; lower lobe solid, with congestion except for upper and anterior margins.

Case X. Sergt. Du. *Haemothorax. Congestion of opposite lung.*

Hit Aug. 4. Shell wound in r. loin running upwards and entering thorax. A tube had been inserted in it. Haemoptysis.

Aug. 5. Heart natural. P. 112. R. 20. T. 99·8°.

Aug. 6. Lungs : a little rhonchus in l., which was otherwise natural. R.

front, rhonchus ; r. back, breath sounds audible at upper part, dull and silent at base. P. 120. R. 36. T. 100°.

Aug. 7. Cyanotic; loud rhonchus over l. front and side; weak breath sounds and râle on r. ditto. P. 128. R. 36. T. 99·4°.

Aug. 8. P. 128. R. 40. T. 100·2°. Over back of l. lung crepitant râle and down vertebral groove bronchial breathing; r. lung tympanitic over scapula, dull and silent below. Death.

Pericardium and heart natural; a little displaced to l. R. pleura held a good deal of blood. R. lung adherent by recent lymph to front wall. Collapsed to size of two fists and congested. Lower lobe of l. lung showed usual appearance of congestion; quite solid at back ; upper and front edges alone contained air. Back of upper lobe in same state. Some haemorrhage about and in substance of r. kidney ; small pieces of shell-case there. No fluid in pleura. No peritonitis.

Case XI. Gnr. Bu. *Haemothorax. Congestion of opposite lung.*

Hit Aug. 7. Shrapnel. Deep wound third r. space ; plugged ; no exit.

Aug. 7. Lungs : l. front and side natural; r. a little breath sound at apex, none at side. R. 36. Much distress.

Aug. 8. Much distress. Removal of plug caused great gush of blood and air. Lungs : l. front breathing well, much sibilus; r. front surgical emphysema with sibilus and râle. P. 128, very weak. R. 32. T. 101·2°. Death.

A large amount of bloody fluid in r. pleura. R. lung adherent to front wall, otherwise free. Collapsed to size of two fists. Large wound in front leading down to broken rib and back, outside which, under scapula, was the missile— a piece of shell. Pericardium and heart a little displaced to l., unwounded. Back of upper lobe of l. lung solid with congestion, the rest of lung natural.

I have given these cases at some length because they exhibit both the chief dangers in the early stage of chest wounds, and the signs which indicate them.

The two chief dangers are :

1. Pneumothorax, indicated by tympanitic resonance and displacement of the heart. The bell sound could not be elicited in some cases where the presence of air was proved by aspiration.

2. Congestion of the unwounded lung, indicated by rhonchus and râle in it.

LESIONS OF THE PLEURA.

Haemothorax is almost always present. In Case IV it did not occur, and in fourteen others the signs did not point to it. In so far as by allowing the lung to collapse it stops haemorrhage it is a salutary event. It varies from an effusion which causes only a small area of dullness and weak breathing at the base to one which reaches the anterior axillary line. Even large effusions are borne without distress and do not greatly displace the heart unless they are complicated by pneumothorax, which may arise either from the original injury or from infection of the effusion by gas-forming organisms. The latter event, which is the chief cause of death at the base, does not usually occur until three or four days at least after the wound.

In five of my cases sepsis occurred before evacuation. They were kept back because their general symptoms led me to suspect it. They were resected on

the fifth or sixth day after the wound, and though four of them were severely ill at first, all were ultimately sent down to the base.

I did not aspirate any cases of simple haemothorax, as I thought it better that the operation, if required, should be done at the base.

In two cases haemo-pneumothorax was causing distress which was relieved by aspiration.

Case XII.   Pte. Sc.

Hit July 20.   Shrapnel; l. axilla.   He was much distressed when admitted, but for the first two days the heart could neither be felt nor heard.   Surgical emphysema obscured the signs in the l. lung.

On the 23rd the r. border of the heart was found close to the r. nipple.   The l. front was tympanitic.   No bell sound.   Aspirated $1\frac{1}{4}$ pints of blood and much air, both sweet.   The heart came back $1\frac{1}{2}''$ towards the l., the pulse dropped from 120 to 88 (July 25), and he was sent down comfortable.

Case XIII.   L.-Cpl. Id.

Hit July 27.   Shrapnel; under l. clavicle.   On admission the heart was impalpable, but the sounds were audible in the natural position.   Breath sounds were weak on the l. side.

July 30.   The r. border of the heart appeared by percussion to be $1\frac{1}{2}''$ to r. of r. sternal edge.   Auscultation bore this out.   Impalpable.   The l. front was tympanitic to the fifth rib.   There was no bell sound, but for a short while there was faint amphoric breathing in the upper three spaces.   The l. back was dull and silent.   P. 120.   R. 36.   T. 102·4°.

July 31.   Same conditions ; distressed.

Aug. 2.   Aspirated 1 pint of blood and much air, both sweet.   The heart after this came in about $1''$ to the l. and he became a good deal more comfortable.   Evacuated to base.

The following were cases with unusual signs :

Case XIV.   Pte. Pa.   *? Local pneumothorax on unwounded side.*

Hit July 30.   Shrapnel: (*a*) inner side of angle of l. scapula; (*b*) exit, anterior axillary fold above nipple.   Haemoptysis.

July 31.   Heart's apex impalpable, sounds inaudible.   P. 96.   R. 60.   Lungs: sibilus over r. lung front and back.   Râle over all l. lung, but impairment at base and sounds very weak.

Aug. 3.   Lungs : r. front natural ; back resonant from top to bottom, but over the base, below the angle of the scapula and between the posterior axillary line and the spine, the breath sounds were entirely absent.   V. R. diminished. P. 76.   R. 36.   T. 99°.

These signs remained unchanged until his discharge on Aug. 6.   The heart's apex was impalpable up to that date, but the sounds became faintly audible on Aug. 5 in the natural position.   On Aug. 6 : P. 76.   R. 20.   T. 87·8°.   The signs were those of a localized pneumothorax, but the situation was extraordinary.

Case XV.   Pte. Bo.   *Pulsating haemo-pneumothorax.*

Hit July 29.   Bullet ; outside l. shoulder.   Haemoptysis.

July 30.   Heart's apex impalpable ; r. border a little displaced to r. (by percussion and auscultation).   P. 100.   R. 32.   Lungs : r. front natural ; l. front, surgical emphysema obscured everything.

July 31.   Lungs : r. back natural ; l. back impaired note, weak breath sounds.

Aug. 2.   Heart: fourth border $1\frac{1}{2}''$ inside r. nipple line.   P. 100.   R. 22. T. 100·4°.   Lungs: very little sound over l. front, none at l. side.   Aspirated with no result.

Aug. 5.   Haematuria began the night before and continued.   No other evidence of damage to kidney.   On l. side an impulse, thought to be due to the cardiac apex, was felt in fifth space.   The usual cardiac dullness seemed to be present.   It was continuous with the impairment of the l. side and back.   The upper front was tympanitic.   There was no breath sound; no bell sound.   *Pulsation was palpable and visible up to clavicle.*   P. 112.   R. 28.   T. 98°.

Aug. 6.   The l. side was bulging a little and there was a slight local prominence under the clavicle.   Pulsation as yesterday.   But to-day the heart was obviously beating on r. side, as far out as nipple line.   The impulse felt in l. fifth space both yesterday and to-day could not therefore be cardiac.   It was the same as the impulse felt in the upper resonant area.   An occasional tinkling sound heard.

Aug. 7.   Same signs, but no tinkling could be heard.

Aug. 8.   Same signs.   Well-marked succussion splash both heard and felt. General condition excellent, though haematuria still remained; no distress. Temperature normal.   Evacuated to base.

Pulsating emphyema is known, but I have never heard of pulsation in a pleura containing air and blood.   When the pulsation was first noticed, my colleagues in the clearing station and I held long consultations over the case. We could think of no known condition likely to produce it except aneurysm. But the impulse was not like that of an aneurysm; there was no bruit, and an aneurysm of that size must have produced distress.   In the absence of any constitutional symptoms pyopneumothorax can be excluded.

The haematuria was difficult to explain.   We searched in vain for any local evidence of renal injury.   The missile to have reached a kidney must have perforated the diaphragm, and that injury is in most cases fatal.   It did not seem at all likely.   There was no evidence of acute nephritis.

There was, however, another remarkable case in which a bullet entering by the chest produced renal symptoms.

Case XVI.   Pte. Pe., aged 22.

Hit July 14.   Bullet; r. second space in nipple line; no exit.   Haemoptysis; signs of r. haemothorax; no abdominal symptoms.

July 19.   Had been passing very large quantities of urine last night and to-day, 4 pints from 4 a.m. to 11 a.m. this morning.   No sugar; no albumen.   Questioned with reference to diabetes insipidus, he said that he always passed much urine, and sometimes got up thrice at night.   None of the cardio-vascular changes of chronic nephritis.

July 20.   Polyuria still.   Haematuria this morning.   Bullet found lying under skin over l. kidney.

And another patient hit low down in the l. axilla passed blood in the field ambulance, though not subsequently.

Both these cases were evacuated in good condition.   I do not know why injury to the kidney should produce polyuria as a prelude to haematuria.

Pneumothorax is occasionally due to a wound in the chest which leaves a free opening.

Cases III and IX are examples of this, and there were two deaths from the same conditions before I began to take consecutive notes of each case.   No form of pneumothorax is other than serious, but this form is the worst because of its

great tendency to become infected from the first. These four cases all died from septic poisoning. When, as in Case VIII, there is a large pneumothorax with excessive pressure, the danger is rather from the distress caused by pressure than from sepsis. In such cases, if aspiration does not materially reduce the pressure, I think the right course is to make a free opening. The operation does not under the usual precautions increase the danger of infection and the pressure is at any rate reduced to that of the atmosphere. The lung on that side will have already completely collapsed and its condition cannot be made worse than it is. The prognosis must always be bad.

LESIONS OF THE LUNG.

The wounded lung usually breathes weakly, and the chest on that side moves less than on the other. Bradford discovered the occurrence of acute emphysema. I have not seen this *post mortem*, but I have often found the praecordial dullness absent and faint breath sounds over the cardiac area in wounds of the l. lung, and have supposed that they were caused by this condition.

Bradford discovered also that in some cases the opposite lung partly collapses. I think I have seen several cases of this.

Case XVII. Cpl. McK.

Hit July 14. Shrapnel: (*a*) lower r. back ; (*b*) r. shoulder. Haemoptysis doubtful ; none on admission.

July 16. Heart's apex 1″ outside nipple line ; sounds natural. P. 96. R. 20. Both fronts moving. Breath sounds a little weaker on l.

July 17. L. base dull ; loud bronchial breathing. Sounds hardly audible at upper back. R. back resonant and breath sounds audible. No fever.

July 18. No fever. Tongue clean and moist. P. 96. R. 20. Bronchial breathing at l. base is less loud ; some crepitations there ; l. front and side natural. R. lung natural.

July 19. No fever. P. 84. R. 20. Bronchial breathing almost gone.

There was no real evidence of injury to the r. lung. If these signs had been caused by the missile going across to the l. base they would hardly have cleared up in the time.

Case XVIII. Pte. Pro.

Hit July 21. Shrapnel ; r. shoulder. Haemoptysis.

July 22. Heart's apex ½″ outside nipple line ; sounds natural. P. 92. R. 30. Lungs : l. front and side and r. lower front all breathing well with a little rhonchus.

July 23. Heart's apex 1½″ outside nipple line.

July 24. Lungs : both bases dull ; r. base silent ; breath sounds in r. upper back ; bronchial breathing at l. base. Very short of breath on moving and became cyanosed. P. 84. R. 24.

July 25. P. 76. R. 24. T. 101·5°. Still could not bear to be moved.

July 26. P. 68. R. 24. T. 99·8°.

July 27. Heart's apex in fifth space just outside nipple line. There was still bronchial breathing at the apex of the l. lower lobe, but the base was breathing with some crepitation. He was much less short of breath.

In a third case a bit of shell had gone in at the l. neck and out at the l. shoulder. On the third day there was bronchial breathing and crepitation at the r. base, though the breathing was quiet and there were no signs of fever. The liver dullness had risen to the fifth rib.

In one case in which a bullet had gone straight through the r. chest, the l. front was silent on admission (second day), but was breathing naturally the next day.

In another seen on the day of the wound, which was by shrapnel, above the r. clavicle, the heart's apex was in the fourth space 1″ outside the nipple and the l. lung was silent in the lower part of the axilla. He was not turned over on that day. The next day the apex was in its natural position and the base of the l. lung was breathing.

In three cases, when the back was first examined, one on the third day, two on the fourth day after the wound, there was loud bronchial breathing at the opposite base without any of the symptoms of pneumonia.

Collapse occurs also on the wounded side. This is more difficult to ascertain owing to the presence of haemothorax. I have noted loss of movement or silence or flattening on the front of the wounded side in four cases on the second day, in eight cases on the third day, and in two cases on the fourth day after the wound.

The following cases are additional and have some points worthy of special notice:

Case XIX. Gnr. Sc.

Hit July 24. Shell; l. lower axilla. Haemoptysis.

July 25. Heart's apex in third space above l. nipple. P. 84. R. 32. Lungs: r. front natural; l. front breath sounds weak.

July 27. Lungs: skodaic resonance below l. clavicle, followed by dullness due to heart from second to fourth rib. Heart was visibly beating in this area. Below this was a line of dullness in which the heart was not palpable and scarcely audible, and at fifth rib stomach resonance. Breath sounds faint at apex. L. back dull and silent. P. 76. R. 32. Comfortable.

July 29. Heart's apex was now palpable in fourth space.

[Continuation note by Captain C. McNeil, Stationary Hospital: L. base dull with weak breath sounds audible; diminished V. R. Heart's apex in fourth space. Aspirated 16 oz.; *Staph. aureus, Strept. brevis,* and a large aerobic Gram-positive bacillus. Pulse, temperature, and respirations never above health standard. In view of patient's excellent condition evacuated 10/8/16 to England.]

I take this to have been a combination of active collapse of the upper lobe and haemothorax.

Case XX. Pte. Ty.

Hit July 29. Bullet: (*a*) second l. space 2″ from mid-line; (*b*) exit about sixth space l. axilla. No haemoptysis.

July 30. Heart's apex 1″ outside nipple line; sounds natural. P. 92. R. 24. Lungs: r. front and side, breath sounds audible with loud rhonchus; l. side, breath sounds weak with moist sounds. Some surgical emphysema in axilla. Not examined behind.

July 31. Heart's apex in mid axilla. P. 104. R. 28. Lungs: r. natural front and back save for rhonchus; l. base dull, with loud bronchial breathing at apex of lower lobe.

Aug. 2. Where in l. back there was bronchial breathing two days before, there were now weak breath sounds with some crepitations. Heart's apex as before. P. 80. R. 28.

Aug. 3. Heart's apex in fifth space 1″ outside nipple line. P. 76. R. 28.

Aug. 5. Heart's apex natural. Back of l. lung was impaired the whole way up, with weak breath sounds and no vocal vibrations.

In this case it seems that active collapse occurred at first and increased on the 31st (third day), and there was haemothorax as well.

Pneumonia occasionally occurs in the opposite lung with the typical symptoms. I had only one such case.

Among the cases which died there was evidence of *congestion of the opposite lung*, even where, as in Case XI, the missile was never near the opposite side. This condition produces rhonchus and râle, and occasionally (Case X) bronchial breathing.

Case XXI. Pte. Ro.

Hit July 15. Bullet; entrance l. second space near sternum, exit l. lower back. Haemoptysis. Heart's apex and sounds natural. P. 124. R. 28. Lungs: r. front natural, râle at side, at base slight impairment and many râles; l. front natural, râle at side. Back impaired above, dull at base. Weak breath sounds and a little râle.

It is so common that it can hardly be called dangerous, but it becomes a danger if it is of large extent and the wounded lung is useless. The condition in its extreme form is illustrated by Cases V, VII, IX, X, and XI. The lower lobe is usually affected alone, in one case the upper lobe too. It may occupy the whole lobe; when it does not, the parts which escape are a margin lying next the fissure and the anterior part. There are often haemorrhages beneath the pleura, especially on the posterior and on the diaphragmatic surfaces. The lung is bulky and heavy, and on section the surface is glistening and deeply red. It is almost or completely airless. I have always looked for evidence of direct injury, but there was none.

I do not understand exactly how this condition occurs. Two explanations suggest themselves: the one, that it is due to the position; the other, that it is due to weakness of the heart. Both would account for it as a form of the hypostatic congestion with which we are familiar in cases of cardiac disease and in other chronic affections.

They do not satisfy me. In the first place, these patients hardly ever lie flat. They are almost invariably propped up on pillows and bedrests. Case IX, for example, sat almost upright. In the second place, though the pulse may be

very weak, it is seldom irregular, and so far as I have seen the heart is not dilated. Thirdly, the condition comes on more rapidly than hypostatic congestion in civil disease.

It may be due partly to deficient movement of the chest wall. Yet on the unwounded side the movements as a rule are large enough, I should have thought, to exercise the lung freely.

However, though no one of these causes alone may suffice, the combination of all or two of them may be more powerful than I have hitherto thought them.

In conclusion I should like to express my obligations to Lt.-Colonel Thompson, and to my surgical colleagues at the C. C. S., Captains Lockwood, Kennedy, Macfie, and Laing, for the opportunity to observe the cases and for the help which they afforded me in the treatment of them.

JAUNDICE OF INFECTIVE ORIGIN

By BERTRAND DAWSON AND WILLIAM E. HUME

With Plates 10–16

THE following account is chiefly based on a study of 178 cases of jaundice which were admitted during nine months to the 14th General Hospital (Lieut.-Colonel Goodwin, D.S.O., C.M.G.) and the 14th Stationary Hospital (Lieut.-Colonel Evans, D.S.O.), to whom our thanks are due for facilities in investigating the cases under their care.

The majority can be classified into one of the three following groups :

    A. Spirochaetal jaundice.

    B. Enteric jaundice.

    C. 'Catarrhal' jaundice (including some indeterminate forms).

(A.) *Spirochaetal jaundice.* Certain Japanese authors[1] have described a disease in which jaundice was a constant feature, and have proved it to be due to a spirochaete (spirochaetosis icterohaemorrhagica). They showed that the blood of these patients caused jaundice in guinea-pigs, and they also obtained spirochaetes from the blood and from the urine of the patients themselves. The disease described by the above authors had the following characteristics :

The illness was ushered in with fever (103°), malaise, conjunctival congestion, anorexia, and considerable prostration. Jaundice usually appeared about the fifth day of the disease, and the temperature fell to normal between the fourth and the sixth day, and in many cases was succeeded by a secondary rise of fever about the end of the second week. During the first week haemorrhages were common, that is, bleeding from the nose, lungs, stomach, bowel, and kidneys. Herpes was common. If the blood from these patients during the first few days of fever was injected into a guinea-pig the latter developed a feverish illness, with jaundice supervening on the eighth day. In some cases the spirochaete could be seen in films made from the human peripheral blood. Further, spirochaetes could be obtained from the urine of the patients themselves up to the fortieth day by centrifuging the urine.

We have been able to observe the disease and the pathological changes produced by the spirochaete in the guinea-pig, and reference to this will be made in a later part of this paper.

As most of our cases were studied before the Japanese work was known to us, the actual demonstration of the spirochaete is lacking in many of them.

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[1] *The Etiology, Mode of Infection, and Specific Therapy of Weil's Disease* (*Spirochaetosis Icterohaemorrhagica*), by Ryokichi Inada, M.D., Yutaka Ido, M.D., Rokura Hoki, M.D., Ranjiro Heniko, M.D., and Hiroshi Ito, M.D. (from the First Medical Clinic of the Imperial University in Kyusu, Fukuoka). *Journ. of Exp. Med.*, March, 1916.

Recently, however, we have obtained the spirochaete from the urine in the vast majority of patients suffering both from the severe and mild types of the disease.

The production of the disease in a guinea-pig by inoculation with a patient's blood can only be effected in the first three or four days of illness, and the cases seldom reach base hospitals at this early stage. Only those cases will be described in which the spirochaetes have been found, or which present a clinical or pathological picture so characteristic as to leave no reasonable doubt that they are identical with the disease described by the Japanese workers.

For convenience of description the cases will be divided into two groups : (1) severe, (2) mild. This is an arbitrary division in which the dividing line is ill-defined, as the two groups merge one into the other, and perhaps the largest number of cases adjoin the line of demarcation.

Group I. Severe Cases.

A general description of eighteen cases in this group will now be given, and will be followed by a detailed account of four cases which were investigated either at operation or post-mortem. The chief signs and symptoms are shown in Table I.

The patients were serving in the trenches when they became ill, and the account of the early stage of the disease is taken either from the patients' descriptions or from notes sent from the casualty clearing hospitals.

The onset was sudden in nine and gradual in nine cases. Those who were overcome suddenly complained of shivering, sudden headache, generalized pains, and a sudden prostration ; as one said, he ' fell out very weak ', or in another instance 'suddenly collapsed at church parade '. A gradual onset was manifested by a general seediness, faintness, headache, anorexia, nausea, and occasional vomiting. At the time of reporting sick the temperature was usually found to be raised to 102° or 103°, and during the first two or three days the patient complained of sickness and vomiting (nine cases), great prostration and lassitude, abdominal and muscular pains. The conjunctivae were injected, and herpes about the lips was frequently observed. Briefly, the patient was seized with an acute febrile illness, with great prostration, often associated with conjunctival injection and herpes.

The jaundice appeared from the second to the seventh day after the onset of illness, and the average day of fourteen cases was 4·4. It appeared first in the conjunctivae and rapidly spread over the trunk and limbs.

On admission to the base hospital (the average day being 8·8) the patients were seen to be ill, and were unusually heavy and drowsy. The jaundice was marked and universal. The tongue was frequently dry and covered with a brownish-white fur : in the majority there was herpes about the lips, which frequently became impetiginous.

The other features of the cases are set out under the following headings and can be seen in greater detail in Table I.

Gastro-intestinal. A dirty tongue and anorexia were common to all ;

constipation was marked, and had usually to be relieved by enemata. The stools so obtained consisted of small scybalous masses, which on being broken were clay-coloured (four) or a light brownish-yellow (nine). In eleven cases there was considerable abdominal tenderness. The whole of the upper abdomen was tender, and it was thought that the point of maximum tenderness was placed just above and to the left of the umbilicus. The liver was tender in proportion to its enlargement. Though vomiting was common at the onset of the illness, it usually ceased before admission, except in the case of the patient from whom a round worm was obtained by gastric lavage.

Haemorrhages. Out of the eighteen cases included in this group fourteen had haemorrhages. Haematemesis occurred in four and haemoptysis in six. Epistaxis was considerable in four cases and slight in two. Melaena was observed in three instances, and in three purpura was marked. In one case there were epistaxis, haemoptysis, and melaena.

The Skin. Besides herpes and jaundice the noteworthy features in the skin were a curious purplish discoloration which appeared on the abdomen, loins, and lower part of the chest in those cases which were most deeply jaundiced. Little complaint was usually made of pruritus.

The Liver. In sixteen out of eighteen cases the liver was definitely enlarged to the extent of about three fingers' breadth, and the edge could usually be felt. It was frequently tender.

The Spleen was palpable in two cases at the time they came under our observation, though in a third the edge was said to have been palpable during the patient's stay in another hospital. From observation at operation and the condition of the organ at post-mortem examination it seems certain that the spleen is not usually enlarged sufficiently to be palpable in this disease.

Lymphatic Glands were sometimes shotty.

Urinary System. The most obvious feature of the urine was the large quantity of bile, which gave the urine in most instances the colour of porter. The bile gradually disappeared in the more serious cases in four to five weeks. Albumin was present in fifteen out of the eighteen cases, for the most part coming down as a distinct cloud on boiling the urine, though at times there was as much as an eighth of a boiled test-tube. The urine was usually free from albumin in three weeks in the patients who recovered. Casts, hyaline and granular, were found in nine of the cases. At times free red blood cells and epithelial cells were seen. The nitro-prusside test disclosed no acetone in the urine of those patients who became comatose prior to death.

Muscular Pains. In twelve cases pains in the muscles of the back, thighs, and legs were considerable.

Nervous System. Frontal headache and aching behind the eyeballs was a constant complaint and was little relieved by antipyretics. One patient complained of green vision. Convulsions preceded coma in two fatal cases.

The Circulatory System. There is nothing noteworthy in an examination of the heart, except that one patient had a temporary auricular fibrillation,

polygraphic tracings of which were recorded. In many instances the atropin test, as devised by Captain Marris, R.A.M.C., was applied, and $\frac{1}{33}$ gr. was administered hypodermically. In this spirochaetal group the heart escaped on each occasion to the extent of 25–50 beats, contrasting markedly with the lack of escape which the heart exhibited in those cases of jaundice which were proved to belong to the enteric group. The pulse-rate is somewhat slow in proportion to the range of temperature.
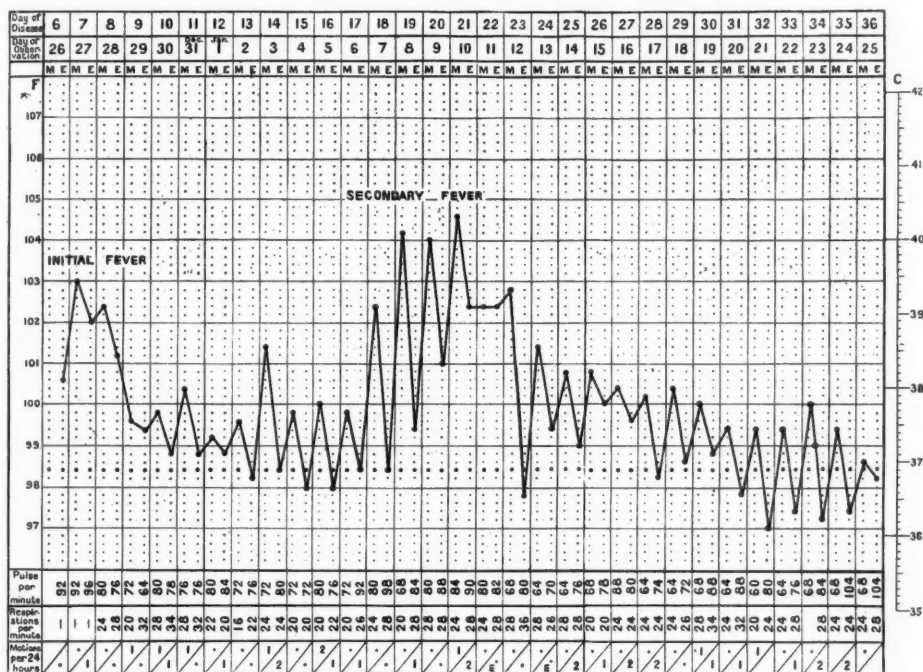
CHART I.

The blood pressure was normal, and again contrasted with the lower pressures met with in the enteric group. Examinations of the peripheral blood were always made. The more serious cases became slightly anaemic, and on one occasion a red count as low as 2,160,000 was found. The white counts for the most part showed a leucocytosis, and in thirteen the white cells were over 10,000 per c.mm. of blood. Differential counts showed that there was a relative increase of the polymorphonuclear leucocytes. The fragility of the red cells was tested on two occasions and was found to be normal. In no instance did the blood films show evidence of such reaction on the part of the bone marrow as would have been expected after blood destruction—that is, no marked variations in size or shape, no polychromasia, and no nucleated red cells were present.

The Fever. The initial rise of temperature has been noted in the description of the onset of the fever, rising usually to 103°. After seven to eight days the

temperature reached normal and usually remained normal for four to five days. In six cases there was a definite period of secondary fever, as shown in Chart I. In the remaining eight cases the temperature rose a little about the fourteenth day and remained at a higher range for some days—a smaller degree of secondary fever (Chart II). Four patients were sent to England as soon as the initial fever waned.

Course of the Disease. At the end of seventeen to twenty days the patients usually showed signs of commencing convalescence, and the average stay in hospital was seventeen to twenty-one days. At the end of three weeks the temperature would usually swing between 97° and 99° p.m., and this mild
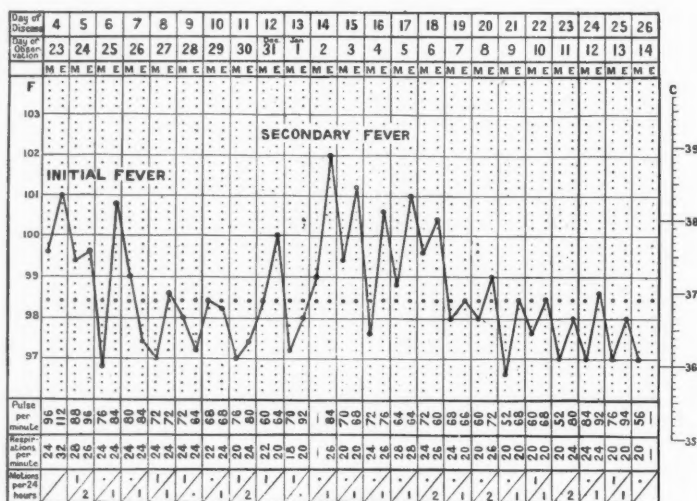
CHART II.

degree of fever continued up to the time of the patient's departure for England, even though he was going about and otherwise seemed perfectly well.

Special Cases.

Table I, No. 1. Aged 38. Began to retch and vomit on November 10, 1915 ; on November 12 he noticed that ' his water was like blood ', and on November 13, feeling drowsy and ill, he reported sick.

On admission on November 15 he looked ill and drowsy. The bowels had not been opened for seven days, which gave rise to considerable abdominal distension and discomfort. There was a thick brown fur on the tongue and marked universal jaundice. The abdominal distension was relieved by an enema, but tenderness in the epigastrium persisted. The liver was palpable and tender, its lower edge extending for two fingers' breadth below the costal margin. No enlargement of the spleen could be detected.

The urine was loaded with bile and a large cloud of albumin appeared on boiling. There were fairly numerous hyaline and granular casts.

The temperature on admission varied between 100° and 102° and fell to 98·6° on the twelfth day of illness; on the thirteenth day it began to rise again, reaching 103·2° on the sixteenth day. This secondary rise lasted till the twenty-seventh day. The pulse varied between 72 and 104 and was of normal volume and tension. The stools were constipated, light brown in colour, and obviously contained some bile. During the first week in hospital the patient was toxic and drowsy.

An examination of the blood showed 5,200,000 red cells per c.mm. and 13,000 white cells. The differential count of the latter showed a normal propor-
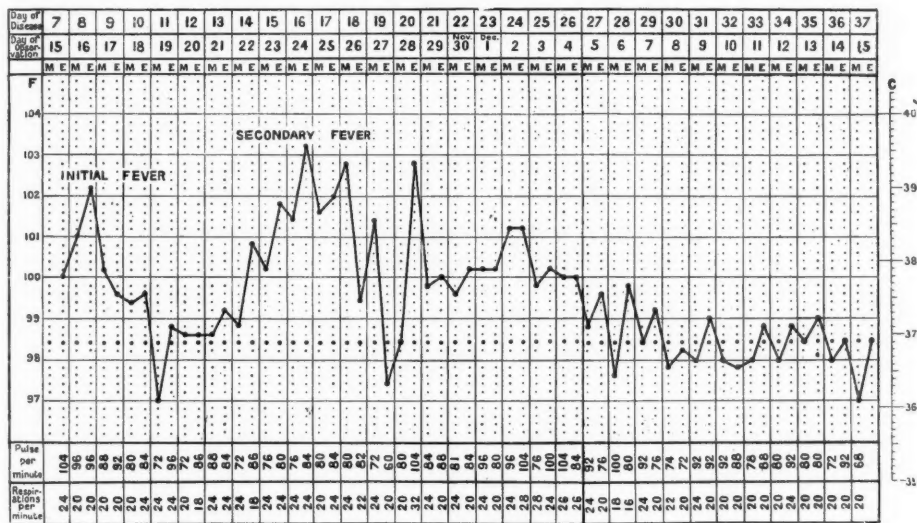
CHART III.

tion of cells: Polymorphs, 63; lymphocytes, 33; coarsely granular eosinophils, 4 per cent.

On November 24 the patient complained of faintness and a feeling of absolute weakness. On November 25 the temperature was 101·8°; pulse 80 and respirations 20. He complained of pain in the feet extending up the shins to the knees. The shins were tender, as also were the calves of the legs.

On November 27 it was decided to open and drain the gall-bladder, and Colonel Andrew Fullerton, C.M.G., A.M.S., performed the operation. The abdomen was opened along the right border of the right rectus and the gall-bladder, which was small and pale, was drained. During the operation the liver was noted to be plum-coloured and 'friable', and a puncture was made into it for bacteriological purposes. There was no shock after the operation, the gall-bladder drained well and the patient improved steadily, and on November 30

the jaundice was considerably less. The tube was removed from the gall-bladder on December 8, and on December 29 the patient left for England. He wrote later and stated that he was very well (January 1, 1916).

Bacteriological Examination of Fluids removed at Operation.

1. *From the liver* was grown a coliform organism which was not agglutinated by the patient's blood serum.

2. *From the gall-bladder* a few colonies of staphylococci.

Table I, No. 4 was taken suddenly ill at church parade and vomited on November 14. Muscular power left him and he was unable to stand, and from November 14 to November 28 vomiting was frequent and he complained of epigastric pain. Jaundice appeared on the fifth day of the disease.

He was admitted to hospital on November 28, and was then intensely jaundiced and in a drowsy state. He complained of spasms of pain across the epigastrium. Constipation was very obstinate and required the use of enemata. The stools were grey-white in colour. There was marked tenderness in the epigastrium, and the edge of the liver could be felt two fingers' breadth below the costal margin. The spleen was not palpable. Examination of the urine disclosed a large quantity of bile, a distinct cloud of albumin on boiling, and very numerous hyaline and granular casts.

On November 30 the patient was drowsy and intensely jaundiced.

On December 1 the gall-bladder was drained by Colonel Fullerton, A.M.S., and at the same time stabs were made into the liver and spleen for bacteriological investigation. Cultures from these showed :

1. *From the liver.* A coliform organism which formed acid and gas with all the sugars.

2. *From the spleen.* A coliform organism which formed acid and gas in glucose only.

The patient died at 2.45 on December 1.

Table I, No. 3 reported sick on December 12, complaining of pains in the legs and vomiting. On that day he vomited half a pint of clotted blood. He remained in his billet for five days and was then sent to hospital. At this time he was very ill and drowsy. He became jaundiced on December 19.

On December 22 the conjunctivae, skin, and mucous membranes showed an extreme degree of jaundice. The abdomen was distended, though not rigid, and there was tenderness in the right hypochondrium. The tongue was coated ; there was no oral sepsis. There was a slight bronchitis and a small quantity of blood-stained sputum. The urine was bile-stained, albumin was present, but no renal casts were found. The stools were semi-solid and clay-coloured.

On December 26 the abdominal distension was very marked and the thoracic viscera seemed to be displaced upwards, the lower part of the left chest moving poorly. The patient was breathless and rather drowsy.

On December 31 the patient was less drowsy and the jaundice less marked, and next day the temperature was normal. The pulse-rate varied between 88 and

96. On January 3 the drowsiness had again increased, and henceforward persisted.

On January 7 there was a general convulsion; the face twitched and there were clonic spasms of the arms and legs. After this convulsion the clinical picture resembled that of diabetic coma; the respirations were increased in range, the temperature was 96·4°, and the pulse 140; the patient could be roused, but quickly relapsed into stupor. Gradually this stupor deepened, passed into coma, and death occurred on January 9. During the last week of life there was a rapid and progressive loss of flesh, and the jaundice continued to diminish.

Table I, No. 2[2] was taken ill with a sudden chill and shivering on December 16. He had to take to bed, and complained of headache, nausea, and pains in both thighs. He frequently felt chilly and had pain in the epigastrium. On December 21 he became jaundiced. On this day there were no abnormal physical signs to be detected in any of the systems except some epigastric tenderness. Vomiting ensued and nothing could be retained in the stomach, and on December 24, while attempting gastric lavage, the patient vomited and a round worm was voided.

During the following week the jaundice steadily deepened in intensity and the urine was deeply bile-stained. The stools were liquid and of a pale yellow colour. Nausea was marked, and there was constant vomiting of small amounts of uncoloured mucus. Daily lavage of the stomach was carried out with no relief.

Except on the first day, when the temperature was 101°, there was no pyrexia, and both the pulse and respiration rates fell to 60 and 16 respectively There was considerable tenderness of the upper abdomen and the muscles were slightly rigid. The liver was enlarged and the edge extended three fingers' breadth below the costal margin. The spleen was not palpable. An examination of the blood showed 34,100 white cells per c.mm., and the differential count was:

Polymorphonuclear leucocytes	93 per cent.
Lymphocytes	6 per cent.
Large mononuclears	1 per cent.

The urine contained a large quantity of bile and one-eighth of a boiled test-tube of albumin. A culture made from the urine was sterile.

The faeces showed some blood, but no parasites, no ova, and no organisms of the enteric group.

In the forenoon of December 29 some twitching of the face and arms was noticed, and about one hour afterwards the patient had a general tonic, and later clonic convulsion. The heart sounds had become very weak, and respiration ceased an hour after the convulsion. During life blood cultures and agglutinations both proved negative to the enteric group.

[2] We were enabled to study this case through the kindness of our colleagues of tho Harvard Unit.

Group II. Mild Cases.

From the foregoing descriptions the impression might be gathered that spirochaetosis always gives this defined picture. This is not so. The majority are less severe in their manifestation, as the following case exemplifies:

Rifleman P., aged 22 years, was admitted to a field ambulance with a slight shrapnel wound of the finger. Two days later (June 16) he was suddenly seized with pains all over the body, headache, and vomiting, and his temperature was found to be 102°. On June 21 there were suffusion and slight icterus of the conjunctivae.
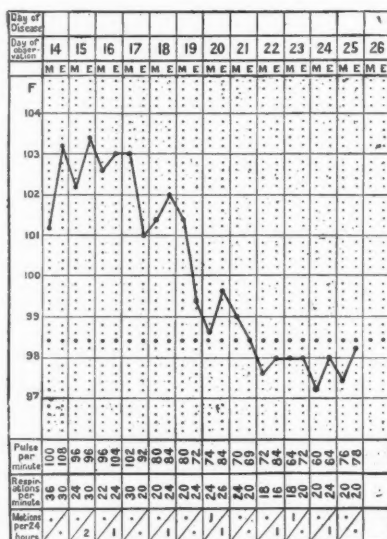
CHART IV.

On June 24 jaundice was marked and the patient was rather drowsy and felt miserable. Physical examination of the abdomen revealed slight tenderness of the liver and no enlargement of the spleen. The axillary glands were just palpable, but there was no glandular enlargement elsewhere.

On June 25 there was general moderate jaundice of the whole body and some skin irritability. The temperature was 98° and the pulse rate 64. The patient was alert and expressed himself as feeling much improved. No enlargement of the liver or spleen could be detected. The white blood cells numbered 8,500 per c.mm. and the percentage of white cells was:

Polymorphonuclear leucocytes	72 per cent.
Lymphocytes	20 per cent.
Large mononuclears	8 per cent.

On the same day $\frac{1}{30}$ grain atropin sulphate was given hypodermically and the heart rate increased from 60 to 90 beats per minute.

Spirochaetes were found in the urine on June 27.

By June 28 the jaundice was fading rapidly, the temperature and pulse rate had become normal, and the patient was convalescent.

A complete analysis has been made of fifty-eight mild cases. It will only be necessary to draw attention to the incidence of the main features and characteristics of this group. This can be most readily shown by the following table :

Synopsis of Fifty-eight Mild Cases.

1. *Onset.* Gradual 42
          Sudden 16
2. *Initial fever* 58
         (Average length of fever six to eight days.)
3. *Conjunctival suffusion and photophobia* . . . 50
4. *Jaundice.* Well marked 51
          Slight 7
5. *Herpes labialis* . . . . 30 (approx.)
6. *Haemorrhage* . . . . Very few.
(There is sometimes sputum tinged with blood early in the case. Unless this is specifically inquired for it would not be mentioned; hence, haemorrhage may have been commoner than this table indicates.)
7. *Abdominal tenderness* 40
8. *Liver* definitely enlarged in 20
9. *Spleen* palpably enlarged in 1
10. *Pains in the back and limbs* 36
11. *Urine.* Bile 58
         Albumin 33
         Casts 10
12. *Stools.* Slate grey 9
         (All stools were *not* examined.)
13. *Red blood cell count* (average) . . . . . $4\frac{1}{2}$ millions
14. *Haemoglobin,* average percentage . . . . 90 per cent.
15. *White blood cell count* (over 10,000) 20
16. *Secondary rise of fever.* Well marked . . . 13
          Slight 8

Inquiry has shown that these patients return to duty at the end of two or three months.

Pathology.

Stomach and small intestine.   Case II died after thirteen days' illness.
The jaundice was intense.   The liver, stomach, duodenum, and upper jejunum
were removed *en masse.*   The mucous membrane of the duodenum was very
oedematous and congested ; its colour was dark blue, resembling a blue plum.
In the first and second portions of the duodenum small yellow patches, varying
in size from pinheads to split peas, were seen through the mucous membrane
(Brunner's glands).   Round the orifice of the bile-duct there was an area about
the size of a florin which was slightly raised above the surrounding mucous
membrane, and in the centre of this area was the ampulla swollen and congested
(Plate 10).   On squeezing the gall-bladder a drop of tenacious bile appeared at the
biliary orifice.   The above features were seen, though in lesser degree, in the
stomach and first three feet of the jejunum.   The rest of the intestines was of
normal appearance.   At the edge of the lesser omentum and about the bile-ducts
were numerous enlarged and soft lymph-glands.

In this case the terminations of the bile and pancreatic ducts were not
opened, but were removed with the papilla and a bit of subjacent pancreas in
order that complete microscopic sections should be made.   The bile-ducts above
their duodenal termination were of normal appearance.

In Case IV the illness lasted seventeen days, and the post-mortem was
performed within four hours of death.   The jaundice was intense.   In this case
the mucous membrane presented the same swollen plum-coloured appearance,
but the papilla was intensely injected, its red colour contrasting with the blue
of the surrounding mucous membrane.   This condition of the mucous membrane,
though most marked in the duodenum, extended to the pyloric half of the
stomach and the upper four feet of the jejunum.   The rest of the intestine was
normal in appearance.

In this case the bile-duct was opened in the portal fissure and a probe
passed into the duodenum.   The duct was opened along the probe.   An incision
was made into the pancreas and the pancreatic duct laid open from that point to
its termination in the ampulla of Vater.   To the naked eye both the biliary and
pancreatic ducts presented quite natural appearances.   They were neither
enlarged nor discoloured, and they presented a striking contrast to the ampulla
and duodenal mucous membrane.   Plate 11 faithfully reproduces the appear-
ances, which suggested that the infection had localized in the duodenum,
stomach, and upper jejunum, and that the jaundice was the result of an
obstructed papilla.   It may be that the duodenal congestion in these cases was
exceptionally severe, but if so it the better makes manifest the process.[3]

In Case III the illness had lasted longer, viz. twenty-eight days, and the
post-mortem was made within four hours of death.   Jaundice was present, but
was moderate in degree.   Here the marked appearances noted in the duodenum
of the foregoing cases were absent, except that the papilla was obvious and slightly

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[3] A similar case is described in the appendix.

oedematous. The common bile and cystic ducts showed no signs of inflammation. There were large glands in the lesser omentum. Death in this case occurred at a later stage of the illness, and it may be that the inflammation of the duodenum had waned.

The microscopic appearances of the duodenum were negative, nor was there any cellular infiltration of the mucous membrane of the ampulla, the congestive swelling of which one would not expect to be shown in the sections. The minute structure of the ampulla is, however, of interest, and Professor Keith, to whom these sections (Plate 14, A and B) were shown, wrote the following note :

'The sections of the ampulla show an anatomical feature of the normal bowel which deserves attention. It is well known that the mucous membrane lining the ampulla is thrown into numerous folds, but I do not remember attention having been drawn to the numerous crypts and recesses lying at the bottom of these folds. Clearly these crypts could afford shelter for the growth and retention of infective micro-organisms. The crypts are excellently delineated by Mr. Ford.'

It is of interest to mention here that in an account of six fatal cases of Weil's disease, recorded by Beitzke (*Berlin. K.W.*, 1916, p. 188) and Herxheimer (*Berlin. K.W.*, 1916, p. 494), no mention is made of a duodenal lesion, except in one case in which it is stated that the mucosa was grey to red brown, the latter colour being especially marked on the summits of the folds.

The Liver. In Case II it was not enlarged, and was firm ; on section it had a greenish tinge, but to the naked eye showed no other change.

In Case IV the liver extended two fingers' breadth below the costal margin and was of a bluish-grey colour. Its cut surface showed dark areas surrounded by pale rings, suggestive of cloudy swelling, but the organ was firm in texture. The intrahepatic bile-ducts appeared somewhat prominent and dilated.

In Case III the liver was enlarged to the same extent as the last case, the texture was firm, and the cut section was of a greenish hue. The lobules were, as in the other two cases, easily distinguished.

In all these cases the gall-bladder was normal in appearance and size, but the bile was unduly thick and tenacious.

In Cases II, III, and IV the liver cells appeared practically normal, and, apart from evidence of biliary stasis, the only abnormal feature was the presence of collections of cells in the portal areas, such as occur in many diseases.[4] In Cases II and III these cells were mainly polymorphs, whereas in Case IV they were mostly small mononuclears, and were less numerous. Staining with Sudan III showed that fat was practically absent from the liver of Case II. The epithelial lining of the small bile-ducts was intact (Plate 13).

In contrast to the foregoing is the following description of the minute structure of the livers from two cases of spirochaetosis, for the opportunity of examining one of which we are indebted to Captain Adrian Stokes.[5]

[4] In this section on minute anatomy we have had much valuable help from Dr. C. H. Browning.
[5] Since this article was written an instructive paper by Capt. Stokes and Capt. Ryle has been published (*Brit. Med. Journ.*, Sept. 13, 1916).

Here (Plate 16, B) the liver cells were dissociated, and many were markedly enlarged and contained well-stained nuclei. Collections of such hypertrophied cells with clear pale protoplasm appeared especially just beneath the capsule. Many liver cells contained two nuclei, and mitoses were numerous. Staining with Sudan III showed a very little fat, in the form of fine droplets, which were partly within the endothelium (Kupffer's cells).

The sum of these changes suggests the effect of damage which has been insufficient to cause extensive necrosis, but has acted as a stimulus to cell growth. In addition, the portal areas show collections of small mononuclear cells and polymorphs, and towards the centres of the lobules both intra- and extra-cellular granules and masses of pigment were found. These microscopic changes resemble those described by Beitzke and Herxheimer. Spirochaetes could not be demonstrated in any of the livers by Levaditi's method.

The Spleen in all three cases was of normal size and consistence, which harmonizes with our clinical observations that enlargement of the spleen is uncommon.

Lymph-glands. The abdominal lymph-glands from Cases II and IV showed a marked accumulation of endothelial cells in the lymph paths, and also numerous polymorphs; many of the former were acting as phagocytes.

Kidneys. Microscopically the kidney in Case IV showed merely the appearances which are ascribed to cloudy swelling. In Cases II and III there were, in addition, scattered areas of cellular infiltration in the cortex, between the tubules and round the glomeruli. In Case II there were haemorrhages into the cortical tubules, and in the latter blood was found in many of the Bowman's capsules. Hyaline casts were seen in all cases. Staining with Sudan III in Case II shows practically no fat in the secreting tubules. Spirochaetes could not be demonstrated by the silver method in any of the specimens.

The Pancreas in all three instances showed no morbid change either to the naked eye or microscopically, and its ducts were normal. This is of interest in view of the relationship which sometimes exists between pancreatitis and bile stasis.

Lungs. In Case II there were numerous subpleural haemorrhages which extended for an inch into the lung tissue beneath, and similar, though smaller, haemorrhages within the right lung. There was no bronchitis. Sections showed extensive collections of polymorphs in and around the areas of not quite recent alveolar haemorrhage, but organisms were not found.

In Case IV there were haemorrhagic areas, $\frac{1}{4}$ to $\frac{1}{3}$ of an inch across, throughout the lower lobes of the lungs.

In Case III there were patches of bronchopneumonia at the bases of each lung, the cellular elements of the exudate being mainly polymorphs, among which scanty cocci in tetrads were seen.

In Cases II and IV there were numerous small subserous haemorrhages over the heart. In Case IV there was a large subendothelial haemorrhage seen inside the left ventricle, involving the upper portion of the septum and extending into the papillary-muscle. In Case II the brain showed no structural change.

The brain was not bile-stained, except the choroid plexuses, which were definitely yellow.

Morbid Anatomy of the Guinea-pig affected by Spirochaetosis.

The most striking features are the jaundice and the widespread haemorrhages which may be seen beneath the skin and serous membranes, in the post-peritoneal fat, occasionally in the muscles, and in the kidneys and suprarenal capsules. The lungs present a specially characteristic appearance, being studded beneath their serous surfaces and throughout their cut sections with these patchy haemorrhages. The liver to the naked eye appears normal.

In three post-mortems the gall-bladder was of normal size; the mucous membrane of the duodenum appeared swollen, but was not congested; the biliary papilla was prominent, and it took a good deal of pressure of the gall-bladder to squeeze bile into the duodenum. We have not, however, examined the duodenum of normal guinea-pigs often enough to be confident of the value of this last observation.

In sections of the guinea-pig's liver, stained by Levaditi's method, the spirochaetes are numerous and between the liver cells (Plate 15, A), in contrast to the human liver, where the spirochaetes are very few and found within the cells. Other sections show dissociation of the cells, many of which were swollen and exhibited autolytic changes. Cells showing two nuclei and also mitotic figures were here and there to be seen. There were also numerous small areas of haemorrhage scattered throughout the lobules and cellular collections—polymorphs and mononuclears—in the portal areas. Staining with Sudan III showed that the liver was practically devoid of free fat.

In the three fatal cases, II, III, and IV, the feature which first attracts attention is the absence of any definite anatomical changes in the liver. Thus, this severe and sometimes fatal infective jaundice is not necessarily associated with structural disease of the liver. It is equally clear that in some cases anatomical changes do occur as one of the results of such infection.

The cause of the jaundice in Cases II, III, and IV cannot be sought in the liver. The common bile-duct, too, is normal in size and appearance. Yet the bile stasis within the liver points either to over-production or to impeded drainage. Over-production would be the result of haemolysis, but repeated examination of blood films failed to disclose evidence of blood destruction, and in two instances in which it was tried the fragility of the blood was normal. The possibility of the jaundice being partly caused by blood destruction has not, however, been exhaustively investigated. A most likely explanation of the jaundice in many of these cases is surely to be found in the obstruction of the swollen papilla, added to increased viscosity of the bile, which was a noticeable feature in three autopsies and two operations. The swelling of the papilla is part of the general congestion of the duodenum and probably subsides when the height of the jaundice is reached, whereas the viscosity of the bile may persist for

a longer period. Whether this thickened bile contained excess of bile pigments there was no opportunity of determining.

The congested duodenum is a local manifestation of the infection, just as the ileum is the usual place for the localization of typhoid.

The increased viscosity of the bile probably played a part in the maintenance of the jaundice, and may explain why the absence of bile pigment from the stools was less marked and prolonged than the intensity of the pigmentation of the skin suggested. The inspissated bile could maintain the back pressure in the biliary tract, but intermittently let enough bile through to partially colour the faeces. This viscosity of the bile must not, however, be looked upon as an invariable factor, for Beitzke observed the bile in his cases to be golden yellow and fluid. With calculus in the common bile duct there may be considerable depth of jaundice notwithstanding the presence of some bile in the stools.

Viewed from the immediate cause of the icterus, Cases II, III, and IV resemble ' catarrhal' jaundice in that they show obstruction of the papilla but not of the biliary ducts; on the other hand, they differ from ' catarrhal' jaundice in the severity of their symptoms. Mitamura [6] describes a case which clinically and pathologically bears the closest resemblance to Nos. II and IV. See appendix, p. 121.

Severe and even fatal jaundice can, therefore, exist sometimes associated with no definite, and at other times with very definite liver changes. The patient dies from the general infection of which jaundice is an incident and the liver changes one of the consequences. This variability in the localization of the lesion is still more marked in another spirochaetal disease, viz. syphilis.

Two of the fatal cases, Nos. II and III, seen in their later stages presented pictures of profound toxaemia such as might have characterized acute yellow atrophy or cirrhosis, yet there was no structural change in their livers. Side by side with this may be placed the observation that cases which show the clinical features of acute yellow atrophy in some instances show *post mortem* the marked anatomical changes of acute atrophy, and in other instances no such characteristic changes. In other words, the toxic symptoms do not primarily depend on the liver necrosis, which is rather an anatomical end product of the causal infection.

If in its course the infection had not localized in the duodenum, should we have had the same clinical picture except for the absence of jaundice ? In other words, how much does the jaundice *qua* jaundice contribute to the toxic symptoms ? Until a fatal case has occurred without jaundice it is perhaps difficult to answer this with certainty. Bile, and chiefly bilirubin, has a toxic effect on animals, and clinically we are familiar with the muscular weakness, nervous depression, slow pulse, and other symptoms associated with jaundice. On the other hand, jaundice itself is slow to produce severe or fatal toxaemia. Witness how tolerant patients are with the deep jaundice of mechanical obstruction, unless there is concurrent infection. Although the jaundice may contribute

[6] Zur Pathogenese des Icterus catarrhalis, *Mitteil. Med. Facult. Kais. Japan. Univ. Tokio*, 1915.

to the toxaemia it cannot be its main cause.   Moreover, in the fatal case, No. III, the jaundice was steadily lessening while the toxaemia deepened.

The same applies to haemorrhage.   Jaundiced patients certainly have a proneness to bleed, but how far this is due to the jaundice and how far to a concurrent infection it is difficult to say.   In many of these spirochaetal cases the jaundice factor is eliminated in that the haemorrhage preceded the icterus.

It occurred to us that the toxaemia of the bad cases might have been contributed to by the supervention of a microbic infection.   To investigate the point we made cultures from the blood and liver punctures in the fatal cases; we punctured the liver of Cases I and IV at operation, and we bacteriologically examined the duodenal secretions.   The results obtained at the autopsies we put aside, for even when the latter are done promptly the presence of coliform organisms may well be the result of impending death.   The finding of coliform organisms from the liver puncture of Cases I and IV cannot be put aside so lightly.

As regards the results of duodenal intubation, although the duodenum may contain coccal organisms in health, we are inclined to think that the presence of coliform organisms is evidence of disease, and such organisms were found in the bile obtained from the duodenum of certain of these cases.   Needless to say, no inference can be drawn from these few observations, though perhaps they are worthy of mention.

Is jaundice a necessary feature of spirochaetal disease?   Though depth of jaundice usually goes hand in hand with severity of infection such parallelism does not always exist.   It is common for a relapse of fever to occur without any interruption in the subsidence of the jaundice; in one case there was a relapse of fever after the jaundice had disappeared, but there was no return of the icterus.   In one of our fatal cases the jaundice was fast disappearing during the last ten days of life when toxaemia was steadily increasing.   These considerations lead one to think that jaundice, though perhaps a usual, is not a necessary manifestation of spirochaetal disease, just as typhoid may exist without intestinal ulceration.

This view received support from the fact that in the units from which the jaundice patients have come there have been simultaneous cases of fever presenting somewhat similar early symptoms but in which no icterus supervened.

Complete confirmation is established by the occurrence of cases of spirochaetosis without jaundice.

Case A was in perfect health until August 25, when he began to suffer from pains in the head, back, and legs.   During the next twenty-four hours he became so giddy that he was unable to go about.   The next day he was sent to the dressing station, where it was found that his temperature was 102°.   He was admitted to a base hospital on August 29.   He then complained of pains in the head and back and of giddiness; there had been no vomiting and no abdominal complaint.   For the first few days of his illness he had a cough; there were no haemorrhages, but there was a herpetic rash on the lips.   As will be seen from the temperature chart (Chart V), the illness was short and the temperature rapidly became normal.

On September 8 he still complained of some pains in the shins at night, but otherwise felt perfectly well.

On August 29 spirochaetes were found in the patient's blood by Lieutenant Bedson, R.A.M.C., and on September 8 spirochaetes were found also in the urine.

Case B. Sudden onset with body pains, frontal headache, photophobia, and vomiting. Temperature on the first day was 104° F., pulse 100, and patient was very ill. Conjunctivae were injected; herpes labialis was present, spleen was not palpable; urine showed on heating a thick cloud of albumin, but no bile. Bilious vomiting was persistent for several days.
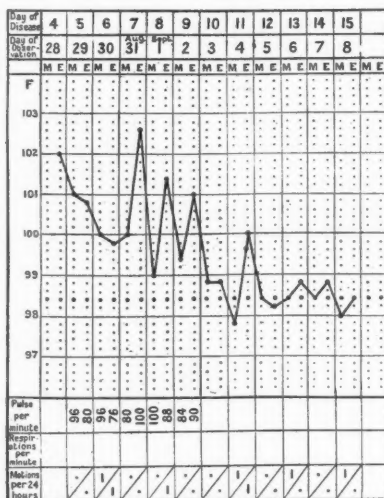
CHART V.

By the fourteenth day the patient appeared convalescent, but on the twentieth day there was a return of fever and pains which lasted for five days. After this, recovery was slow but continuous. Nine weeks after the onset spirochaetes were still present in the urine though health was nearly re-established. At no time was there either jaundice or bile pigment in the urine.

On the third day of illness 2½ c.c. of the patient's blood were injected into the peritoneal cavity of a guinea-pig, which subsequently developed jaundice, and after death spirochaetes were to be seen in the sections of its liver.

For most of this record we are indebted to Captain H. Carson, R.A.M.C.

Case C was suddenly seized with general pains and chilliness. He was admitted to a clearing hospital on the third day and was then extremely ill. Headache and backache were severe, weakness was pronounced and vomiting frequent; the temperature was 103°, the pulse 108, and respiration 30. There were neither haemorrhages nor herpes. The liver and spleen were not demonstrably enlarged. For four days the temperature remained high, but on the fifth day it fell to 99·8°, and on the tenth day to normal, and remained

so. Convalescence was rapidly established, and by the fourteenth day the patient was well enough to return to England.

The patient was never jaundiced, and though there was a suspicion of bile in the urine at the clearing hospital there was no trace of it subsequently. On the third day of illness 5 c.c. of the patient's blood were injected into a guinea-pig, which became ill and developed jaundice, and *post mortem* showed the characteristic haemorrhages in the lungs, liver, kidneys, peritoneum, and skin.

It is of interest to recall that acute yellow atrophy can occur without jaundice. Rolleston (*Diseases of Liver*, p. 587) relates such a case which is worth giving here. On the first day the patient suddenly felt pain and vomited a little blood, on the second and third days there was haematemesis, and on the fourth, fifth, and sixth days melaena. On the second day the liver dullness was diminished. The temperature was usually between 99° and 100° F. The patient became progressively weaker and drowsy and died on the eighteenth day. There was never any jaundice. Examination of the liver *post mortem* showed acute yellow atrophy. There is an interesting resemblance between this case and some of those we have recorded above.

The evidence suggests that this spirochaetosis causes either a septicaemia or a toxaemia; that it has a tendency to fall with greater force on certain, though not always the same organs; that it frequently selects the upper part of the gastro-intestinal tract and liver, and that, as a result, jaundice is a common feature; that in some cases the stomach, or it may be the ileum, is involved and the duodenum escapes, or again the brunt of the disease might fall upon the respiratory tract. In short, it would seem probable that this spirochaetosis must be added to the list of fevers independently of the presence of jaundice. It is to be admitted, however, that the explanation of the cause of the jaundice still lacks completeness.[7]

It is regrettable that the Japanese workers have perpetuated the name ' Weil's disease '. This title was hardly justified, for the condition had been described by the French under the more comprehensive title of ' Infectious Jaundice ' prior to the publication of Weil's cases.[8] Weil's disease is one of many varieties of infection characterized by jaundice and associated by some authorities with *Bacillus proteus fluorescens*. Nor do the clinical features of Weil's disease closely conform with those of spirochaetal jaundice. In the former the onset is sudden, the pulse rapid at the commencement, and splenic enlargement an outstanding feature; whereas in the latter the onset may be either sudden or gradual, the pulse is usually of moderate frequency (about 100 or less), and splenic enlargement is infrequent.

If the term ' Weil's disease ', as has often been the case, is employed to denote any form of infectious jaundice, confusion results, and doubtless typhoid and paratyphoid fever have often been thus disguised.

[7] Later experience in the shape of further examples confirms the occurrence of spirochaetosis without jaundice, and this fact is one to be borne in mind when investigating a pyrexia of uncertain origin.

[8] Chauffard, *Traité de Médecine*, Bouchard and Brissaud.

In this connexion it is interesting to note that under the title *Typhus hépatique bénin, rechutes, guérison*, Mathieu, in 1886, described symptoms suggestive rather more of spirochaetosis than of typhoid. A young man was suddenly seized with shivering, fever, headache, and repeated vomiting. On the fifth day there had appeared icterus, enlargement of the spleen, albuminuria, and purpura. By the ninth day the temperature was normal and the patient had improved. On the eighteenth day there was a relapse of fever and symptoms, lasting a week. After this recovery was uninterrupted.

(B.) *Enteric jaundice.* Jaundice is an uncommon feature of enteric fever. In this campaign its incidence has been rather larger than in some other collections of cases. Thus, it has been 1·38 per cent., whereas in the cases mentioned by Osler and Macrae it was 0·53 per cent. Our figures are, however, not strictly comparable, partly because paratyphoid accounts for most of our cases, and partly because improved methods of diagnosis rope in cases which would previously have passed as 'catarrhal' jaundice.

The following statement is based on twenty-six cases. In addition one case of portal pyaemia will be described. The twenty-six cases may be divided into two groups, one in which the jaundice occurred early, i. e. before the tenth day, and the other in which it occurred later in the disease. Of the total cases typhoid accounts for six, paratyphoid A for four, and paratyphoid B for fourteen.

In one (Case XII, Table III), the variety of enteric [9] could not be determined. In another (Case XI, Table III) paratyphoid B was obtained from the stool in the early part of the disease, and during the relapse paratyphoid A was obtained from the blood.

All the patients had been protected against typhoid, and of these three against paratyphoid as well. There were two deaths, one due to portal pyaemia, and the other a case of paratyphoid B who had been inoculated against typhoid only six weeks previously.

The jaundice presented every grade from deep to faint pigmentation. When severe it made the patients more drowsy and toxic. Otherwise it appeared to have little effect upon the course of the illness, and if occurring later in the disease it was not necessarily associated with a return of fever or an exacerbation of symptoms.

Of the early symptoms headache is the most constant and vomiting is common. Pains in the abdomen, back, and legs, and diarrhoea may also be present. The following figures show the frequency of the early symptoms in the twenty-six cases : Headache, 19 ; vomiting, 12 ; abdominal pains, 8 ; pains in back and legs, 8 ; diarrhoea, 5 ; shivering, 2 ; extreme lassitude, 2 ; and epistaxis, 1.

In Group I (Table II), where jaundice occurs early, the onset is usually sudden, viz. eleven out of fourteen cases. This fact makes diagnosis more difficult, especially if the duration of the fever is short. This is well illustrated

[9] Throughout this article the term 'enteric' is used to denote the group typhoid and paratyphoid A and B.

by Case IV, later described in full, which might easily have been taken for 'catarrhal' jaundice.

In Group II (Table III) a gradual onset is more usual, viz. nine out of twelve cases.

In both groups the features which are associated with the typhoid fever of former days are blurred or absent. Thus abdominal distension was slight or absent; spots were noted in only four cases and the spleen palpable in only four patients. There were relapses in ten cases.

The bacteriological observations, as the tables will show, were very complete. Most of them were made at the laboratory (Captain Perry) of the 14th Stationary Hospital, and some by Lieutenant Bedson.

It will be noticed that their conclusions are chiefly based on the agglutinations. In such cases as these, blood cultures could seldom be obtained early enough to be of use, and one of the results of preventive inoculation is to diminish the likelihood of finding the organisms in the stools and urine. The following cases are illustrative of jaundice occurring early in the illness (typhoid, paratyphoid A and B fevers):

Typhoid fever. Case I, Table II, was seized with a sudden pain across the abdomen while 'throwing up' sandbags on March 31. This pain continued during the rest of the day and night, and the following evening he vomited. The third day he was sent to the field ambulance, where he was told that he was jaundiced.

During the first week of illness he had a continual pain in the abdomen and the bowels were constipated. The fever was not high. On the eighth day the patient was intensely jaundiced and rather drowsy; the tongue was dry and coated with a brown fur: the temperature was 98·8° and the pulse-rate 70; the abdomen was distended and there was a feeling of resistance in the right hypochondrium. The edge of the spleen could be felt a hand's breadth below the left costal margin and the liver edge three fingers' breadth below the ribs. The urine was loaded with bile and urates; there was a large cloud of albumin and a few bile-stained casts. The motions were constipated and of a light yellow-brown colour. The white cells of the blood numbered 4,000 per c.mm. on the eighth day and a differential count showed:

Polymorphonuclear leucocytes	.	.	.	.	62 per cent.
Lymphocytes	.	.	.	.	26·6 per cent.
Large mononuclears	.	.	.	.	11·2 per cent.
Coarsely granular eosinophils	.	.	.	.	0·2 per cent.

During the following five days the patient improved considerably, and by the thirteenth day the jaundice had largely faded, and on the nineteenth day had disappeared.

On the twenty-second day the white cells had risen to 5,800 per c.mm., and the differential count showed:

Polymorphonuclear leucocytes	.	.	.	.	74 per cent.
Lymphocytes	.	.	.	.	24 per cent.
Large mononuclears	.	.	.	.	2 per cent.

On the twenty-fourth day the spleen was still palpable though the patient was convalescent. On three occasions, on the twelfth, fourteenth, and twenty-fourth days of disease, $\frac{1}{30}$ grain of atropin sulphate was administered hypo-

dermically, and the heart-rate was increased so slightly that on this fact alone a provisional diagnosis of 'enteric group' was based.

12th day	.	.	.	62–66	escape	. . .	4
14th day	.	.	.	76–78	,,	. . .	2
24th day	.	.	.	80–86	,,	. . .	6

Chart VI records the experiment carried out on the twelfth day, and contrasts markedly with Chart VII, which was compiled from a case of spirochaetal jaundice. In its onset and clinical features this case was very similar to cases of spirochaetal jaundice of moderate severity. The points of distinction were— (1) the considerable enlargement of the spleen; (2) the refusal of the heart to quicken after the injection of $\frac{1}{30}$ grain of atropin sulphate; (3) the bacteriological proof of infection by the *Bacillus typhosus* by agglutination.
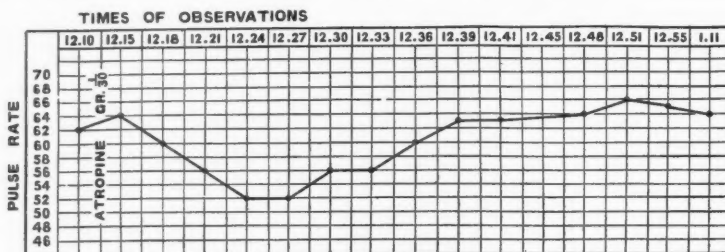
CHART VI.

Case I, Table II. Atropin experiment. Escape of heart = 62-66 = 4.
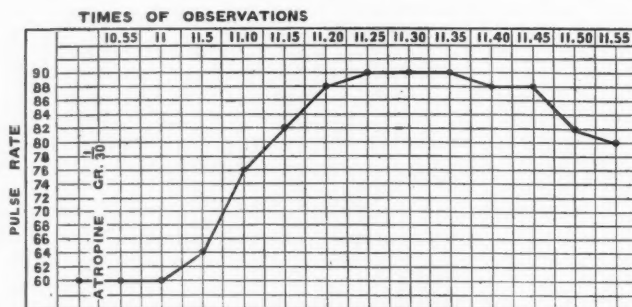
CHART VII.

Case VI, Table I. Atropin experiment. Escape of heart = 60-90 = 30.

Case IV, Table II, aet. 22.[10] There was a sudden onset with extreme lassitude and headache which forced him to bed within a few hours. On the second day there were pains in the head, legs, and across the abdomen, and the temperature was 103·6°. On the fifth day there was repeated vomiting, with which streaks of blood appeared, and icterus, which had shown itself on the previous day, had become definite. By the sixth day the jaundice was deep, though the temperature had fallen and the pulse-rate was 88; the abdomen was flat but tender in its upper half; the spleen was not enlarged, but the liver extended three fingers' breadth below the costal margin; no herpes; the glands were shotty; the patient was apathetic and drowsy. The next day the apathy continued and there was vomiting. On the eighth day the white cells were 23,800 per c.mm.,

[10] We are indebted to our colleagues of the 3rd Canadian Hospital for notes of this case.

the red cells 4,800,000, and the haemoglobin was 80 per cent. Films showed the red cells to be normal. On the tenth day there was still apathy; the tongue was dry in the centre and furred at the side; the spleen was enlarged to percussion, but not palpable; the urine had a specific gravity of 1011, was acid, contained bile and numerous hyaline and granular casts, a few red blood cells, but no albumin. The casts had disappeared two days later and a trace of albumin had appeared.

On the fifteenth day the patient's condition had improved; the jaundice, though still marked, was diminishing; the spleen, however, had become distinctly palpable. Blood pressure was 118 systolic and 58 diastolic. In spite of a slight rise of temperature on the sixteenth day the patient's condition steadily improved and the jaundice faded. On the tenth day, after the injection of $\frac{1}{30}$ grain of atropin, the maximum acceleration of the heart was only six beats (70 to 76) in 50 minutes. On the sixteenth day the same dose of atropin produced an escape of twenty-four beats (68 to 92) in half an hour.
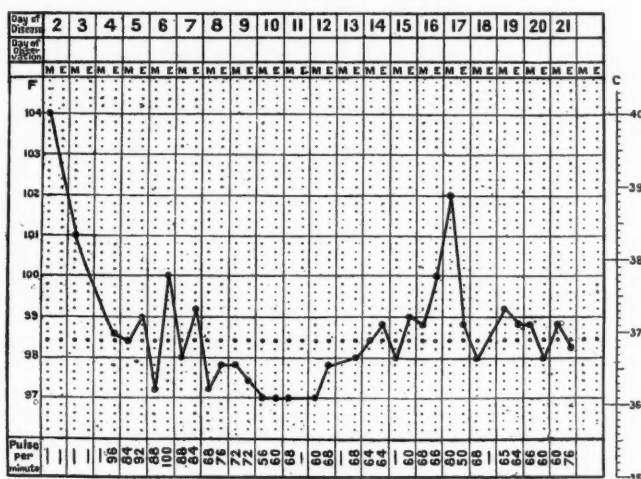
CHART VIII.
Temperature chart from Case IV, Table I.

The difference in these two observations illustrates what Captain Marris has pointed out—that the locking of the heart under atropin in the enteric group may be limited to a few days, the favourite period being about the tenth day.

Duodenal intubation. This was accomplished easily on the sixteenth day. The biliary fluid obtained was reported on by Major Rhea as follows : ' A clear bilious fluid from which no organisms were grown.'

This patient had been inoculated against typhoid twice in May, 1915, but not against paratyphoid.

Bacteriological cultures from the blood, stool, and urine were negative. Agglutinations on the eighth day showed a big rise in typhoid, viz. 1 in 2,500, rising after delay to 1 in 3,675. On the sixteenth day the agglutinations had fallen to 1 in 2,822. Paratyphoid A and B were negative to 1 in 5.

The conclusion from these observations is an infection by the *Bacillus typhosus.* Investigation was made for spirochaetosis; a guinea-pig was

injected with the patient's blood on the sixth day, but with negative results ; the urine was examined twice for spirochaetes, the last time on the seventeenth day, and with negative results.

This case is of interest, for it might so easily be mistaken for either spiro-chaetal or catarrhal jaundice. The acute onset, lassitude and pains, the slight haemorrhage on the fifth day, the jaundice developing as the temperature fell, the shotty glands, could so justly point to spirochaetosis ; and if the atropin test had not been applied till the sixteenth day the escape of the heart might have been an argument against enteric fever. On the other hand, the very brief period of fever, the flat abdomen, and the absence of splenic enlargement in the early part of the illness might well have led to a diagnosis of catarrhal jaundice. Such cases suggest the wisdom of watchfulness that a diagnosis of ' catarrhal jaundice' does not disguise enteric fever.

Case VI, Table II, is an example of jaundice complicating *paratyphoid A*. The patient was suddenly seized with pains all over the body on April 16, 1916, and became weak and prostrate. He was sent to hospital and for the first three days of his illness he vomited frequently. On the fourth day jaundice was first noticed in the conjunctivae, and during the next two days the whole body became intensely yellow. On the sixth day he complained of an aching all over the body and was rather drowsy; the jaundice was intense ; the tongue was coated with a thick brown fur and there had been constipation for three days. The liver edge was felt three fingers' breadth below the costal margin. The spleen was not palpable, but may have been slightly enlarged to percussion. There were no haemorrhages, purpura, or petechiae. The urine was loaded with bile, but there was no albumin,

By the eleventh day, there was considerable improvement in the general condition and the jaundice was beginning to fade. There was never more than an evening rise of one degree of temperature (99·4°), and the pulse-rate varied between 54 and 72. Henceforward there was steady progress towards recovery.

On the seventh day a blood count showed white blood cells 6,800 per c.mm.

Differential count :

Polymorphonuclear leucocytes	.	.	.	60 %
Lymphocytes .	.	.	.	.	20 %
Large mononuclear cells .	.	.	.	17 %
Coarsely granular eosinophils .	.	.	.	6 %

On the seventh day, after $\frac{1}{30}$ grain of atropin sulphate hypodermically, there was a moderate escape of 12 (72–84). Perhaps by the tenth day there would have been a lock, but unfortunately no further observation was made.

By agglutination this case was diagnosed as paratyphoid A.

The following is an example of infection by the *Bacillus paratyphosus B* :—

Case VIII, Table II, reported sick on April 23, 1916, complaining of pains in the legs, which were so bad that he was unable to stand. Later he vomited. At the onset of the illness the temperature reached 104°. On the third day jaundice appeared in the conjunctivae and rapidly spread all over the body. On the seventh day the temperature was 101·2° and the pulse-rate 96 ; the patient was deeply jaundiced and drowsy and complained of a general aching. The liver extended three fingers' breadth below the ribs ; the spleen could not be felt, but the splenic region was very tender.

On the eleventh day the temperature began to rise and the patient became

worse. He was more drowsy and in a condition of misery : there were bronchitic râles throughout both lungs and the pulse was markedly dicrotic. He remained very ill for three weeks, during which he passed through a serious relapse, associated at its commencement with an increase in the jaundice.

About the twenty-first day the jaundice began to diminish and the symptoms to improve, and at the end of five weeks of illness convalescence was established.

On the seventh day the urine was loaded with bile, and showed a large cloud of albumin and a few bile-stained casts ; and on the same day an examination of the blood showed white blood cells 6,100 per c.mm. and differential count :

Polymorphonuclear leucocytes . . .	62 per cent.
Lymphocytes . . . . . . ,	18 per cent.
Large mononuclear cells	20 per cent.
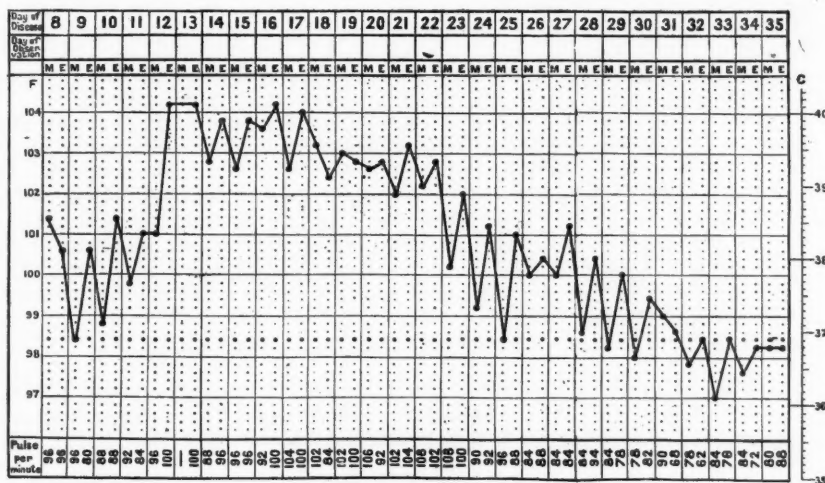
CHART IX.

Temperature Chart from Case VIII, Table II.

On the eleventh day $\frac{1}{30}$ grain of atropin sulphate was injected and the rate of the heart only quickened four beats—from 100 to 104.

Group II, in which jaundice appears later in the disease, is illustrated by the two following cases :

Case IV, Table III. On or about March 1 the patient began to suffer from headache and a feeling of weariness, and shortly afterwards was troubled with diarrhoea.

He was admitted to hospital about the twentieth day of his illness. He was then slightly flushed, but not ' toxic ' ; there were some typical spots on the abdomen ; the spleen was enlarged to percussion and the pulse was dicrotic.

On the twenty-first day the patient had a rigor ; on the twenty-sixth day the conjunctivae were yellow. For eight days the fever had been high and there had been two distinct rigors. After this the temperature became normal and the general condition of the patient improved. The jaundice only lasted ten days, and during the time it was present there was some tenderness in the region of the gall-bladder.

As the jaundice was disappearing the patient had a third rigor.   After that convalescence became established.

The *Bacillus paratyphosus B* was found in a stool and the agglutination curve was convincing.   The clinical picture suggested that the gall-bladder was involved by the infection.

Case V, Table III.   About March 18 this patient complained of pain in the left side.   At that time he suffered much from constipation.   On admission to hospital on the fifth day he was found to have a temperature of 101·2°, and vomited.

During the first seven days the temperature remained high (about 103°) and the patient was ill and drowsy.   There was almost a complete absence of physical signs.   The tongue was coated with a thick white fur, and he complained of frontal headache.   On the tenth day an urticarial rash appeared on the arms and abdomen.

On the twenty-fifth day the temperature rose a little, after having been previously normal for a few days.

On the thirty-first day of disease slight conjunctival and general jaundice was noticed, which began to fade three days later, and on the twenty-eighth day had almost disappeared.   Thereafter convalescence was established.

In Case X, Table III, jaundice was the first, though a late indication of illness.   A nurse was admitted to hospital for a small burn.   Some days later there was a tinge of jaundice and the temperature was found to be 100° F. The pigmentation of the skin deepened and the fever continued.   The spleen was not enlarged and there were no spots.   The patient had only been inoculated against typhoid and the agglutination was positive to paratyphoid B. Inquiry disclosed the fact that for three weeks prior to the burn the nurse had suffered from headaches, loss of energy and appetite, but had kept at her work.

What is the immediate cause of the jaundice in these cases?   There must be some obstruction in the course of the biliary tree.   The symptoms are not severe enough for there to be involvement of the smaller ducts within the liver.   In the only post-mortem (Case IX, Table III) there is no mention of morbid change in the liver or of cholecystitis, and the gall-bladder was distended with clear bile. With the exception of Case IV, Table III, there is nothing in the clinical pictures of the cases under consideration to suggest the existence of cholecystitis.   On the other hand, in most of the instances of cholecystitis complicating enteric fever which have occurred at the 14th Stationary Hospital jaundice has been absent.

The onset of the jaundice in the cases of Group I (Table II) bears a resemblance to those spirochaetal cases in which there was obstruction at the biliary papilla.

The conclusion is that the jaundice is due to a duodenal inflammation, which, in its turn, results from the localization of the infection in the duodenum. Many of the cases described in this paper have been intubated and the duodenal fluid has contained numerous polynuclear cells of inflammation.   On the other hand, typhoid and paratyphoid organisms have not been isolated from the duodenal contents at the 14th Stationary Hospital, though the results of such a search have been positive in the hands of some continental and American observers.

A rarer and more grave form of enteric jaundice is due to suppurative pylephlebitis, and is illustrated by the following example.[11] The illness began with anorexia, abdominal pain, and constipation. On the eleventh day the temperature was 102°, the patient looked ill and was slightly jaundiced, and there were a few suspicious spots. The spleen was not enlarged till the twenty-third day, and then it only showed an increased area of dullness.

From the eleventh day to the twenty-fifth day there was constant abdominal pain, with high fever, rising pulse-rate, increasing abdominal distension, and toxaemia.

On the twenty-sixth day a mass was felt in the right iliac fossa and jaundice was deepening. At operation a shut-off abscess was found in the appendix region. There was no abiding improvement from the operation; the fever persisted, jaundice deepened, and the patient died on the fifty-eighth day.

At the post-mortem there was peritonitis; Peyer's patches were prominent, but there was no ulceration. The appendix was long and the last half-inch was gangrenous. The liver was enlarged and riddled with small abscesses. The gall-bladder was not enlarged, but its wall was thick and the bile was clear. One liver abscess had penetrated the right diaphragm towards the end of life, and had caused an abscess in the lower lobe of the right lung.

During life, one blood culture, three stool cultures, and one urine culture were all negative; yet post-mortem cultures from the gall-bladder and from an abscess in the liver grew *Bacillus paratyphoid B* in pure culture.

(C.) *'Catarrhal' jaundice.* There have been many cases scattered through the hospitals conforming to the features associated with the loosely employed title 'catarrhal' jaundice. Some of them have resembled the symptoms of those described in the foregoing series, from which they have been excluded by negative bacteriological findings. For instance, a patient in the next bed to Case III, Table III, presented the same clinical picture, except that the latter had an enlarged spleen and the former had not. The latter was bacteriologically positive (paratyphoid B), and the former was negative.

'Catarrhal' jaundice has the features of an infection—either a mild blood infection which has localized in the duodenum, or less often perhaps an infective gastritis which has extended to the duodenum. It is a convenient term to describe a jaundice in which the infective agent has not been discovered. The usual symptoms are—headache, lassitude, a transitory mild fever, discomfort in the upper abdomen, anorexia and nausea, with jaundice supervening later. No doubt the same infections can exist without the jaundice.

There have been examples of the well-known association between jaundice and influenza and lobar pneumonia. One case occurred during the peeling stage of scarlet fever. On the twenty-fifth day the temperature rose suddenly from normal to 102°, and there was anorexia with abdominal discomfort. The following day the temperature had returned to normal, but the patient was jaundiced and remained so for nine days.

The following is an example of an undetermined infective jaundice, and as the case was thoroughly worked out it is worth giving in some detail:

Onset was gradual with chilliness, fever, weakness, anorexia, abdominal pain, and vomiting. On the fourth day patient declared sick and the temperature was 108°. On the fifth day the temperature was normal and jaundice appeared. The upper half of the abdomen was tender and the spleen could be felt for $1\frac{1}{2}$ inches below the costal margin. The jaundice rapidly became deep, but,

[11] Dawson and Whittington, *Quart. Journ. Med.*, Jan., 1916.

though apathetic, the patient never was toxic. The urine contained bile and a trace of albumin.

On the ninth day the jaundice was slightly less. On the tenth day there was a return of fever and the spleen remained palpable, but there was no deepening of the icterus. The temperature did not finally settle till the eighteenth day ; the jaundice and the enlargement of the spleen had disappeared on the twentieth day, and by that time convalescence was established.

The atropin test was made twice—on the sixth day, when there was an escape of 20 (60–80), and on the fifteenth day, when there was an escape of 16 (66–82).

Agglutinations were tested three times—on the ninth, fourteenth, and nineteenth days. They were negative to paratyphoid A and B, and typhoid remained constant at 1 in 125. The patient had been inoculated against typhoid only two years previously.

A blood culture was made during a relapse of fever and two cultures, each from urine and faeces, were negative to the enteric group. On two occasions the urine was thoroughly searched for spirochaetes, but with negative results.

The fasting stomach and duodenum were intubated. Cultures from the gastric contents were negative, while those from the duodenal contents showed a growth of a Gram-negative coccobacillus. The characters of this bacillus were tested by putting it through broth, gelatine, agar, litmus milk, litmus whey, peptone, and the sugars. Litmus milk and whey became alkaline in twenty-four hours without clot formation in the former. The sugars were not acted upon, with the exception of glucose, from which acid without gas was formed after forty-eight hours' incubation.

This coliform organism was the sole positive result from the investigations. It was not agglutinated by the patient's own serum, though this is not conclusive against specificity. Was this organism the cause of the illness ? Coliform organisms are known to be associated with cholecystitis and gallstone formation, why not with duodenitis and cholangitis ?

It is doubtful if coliform organisms exist normally in the duodenum. Proof that this organism was the cause is, however, lacking, The alternative explanation is that the patient had enteric fever. The bacteriological findings are against this view. That, however, cases of enteric fever do occur in which the most careful and repeated bacteriological investigations are negative, is undoubted. An example is afforded by the case of pylephlebitis above described.

Diagnosis (Early). An initial difficulty arises from the fact that so many infections have the same symptoms at the commencement of the illness. Given a patient who has head and body aches, chilliness, fever, vomiting, and he may have one of many infections, e.g. enteric, trench fever, spirochaetosis, influenza, Micrococcus tetragenus, amongst others determined or undetermined. The difficulty is less if the onset is gradual, for that would suggest enteric or spirochaetosis. Both these diseases, however, can commence abruptly ; and as regards enteric the proportion of sudden onsets is increasing. Earlier in the war the gradual onset was about twice as frequent as the abrupt one, whereas recently this proportion has changed. Thus an analysis of 136 recent cases shows :

	Gradual Onset.	Sudden Onset.
Typhoid . . .	22 . . .	39
Paratyphoid A . .	30 . . .	14
Paratyphoid B . .	19 . . .	22

As regards influenza, a tentative early opinion can be formed, for the disease seldom exists without the characteristic catarrhal manifestations in the upper respiratory tract.   It is relatively uncommon in the Expeditionary Force.

Trench fever gives no distinguishing early picture.   The characteristic temperature chart and leg pains need to be observed before an opinion can be formed.

Tetragenus infection, if alone, would seem to run but a short course of three or four days.

No doubt if blood cultures could be taken promptly, positive results would be forthcoming in a proportion of cases; but this is impossible where patients are numerous and conditions difficult.

Some assistance in determining the group to which a case of jaundice belongs may be obtained by studying the result on the rate of the heart of the injection of atropin sulphate.   This method of differentiating between 'fevers' belonging to the enteric group and other 'fevers' was suggested by Captain Marris, R.A.M.C., who is publishing a preliminary report on his work.   During an investigation of the cardio-vascular conditions in the enteric group, he found that the heart-rate did not usually quicken after the administration of $\frac{1}{50}$ grain atropin, as the normal heart does.   If atropin sulphate, $\frac{1}{50}$ to $\frac{1}{30}$ grain, is given hypodermically to a normal person, after an interval of 15–20 minutes the rate of the heart will increase to 20–25 beats per minute.   Captain Marris found that for a variable period during the course of typhoid or paratyphoid fever the heart either failed to quicken at all or did so very little after the hypodermic injection of $\frac{1}{30}$ grain atropin sulphate.   After the study of a large number of cases, he is of opinion that the poison of the enteric organisms prevents the heart responding to the action of atropin, and that this effect is most marked between the eighth and fifteenth days of the disease.   The effect may be very evanescent, and may only be present on one or two days; for instance, Case IV, Table II, described above.

The method of administration is as follows: The patient lies absolutely quiet, and ought not to be disturbed during the experiment.   The pulse-rate is counted two or three times, and when it is found that the rate remains constant, $\frac{1}{50}$ or $\frac{1}{30}$ grain atropin sulphate is injected hypodermically.   The rate of the pulse is then counted at intervals of five minutes for an hour.   Normally at first there is frequently some slowing of the heart-rate, and then the speed quickens, usually increasing by 20–30 beats per minute.   The higher rate is usually maintained for about a hour, and then gradually falls back to the normal.

Charts VI and VII (p. 110) show the results of two experiments.   In one the rate of the heart was only increased by four beats, and this 'locking' suggested that the particular case of jaundice was suffering from typhoid or paratyphoid fever.   The agglutination curve was typical of B. typhosus infection.

In the second the heart 'escaped', and increased its speed by 30 beats after the injection of atropin sulphate.   This quickening under the influence of atropin made it probable that the patient was not suffering from any member of the enteric group, and spirochaetes were found in the urine.

After a considerable experience in the use of atropin in the study of bradycardia and other arrhythmias, and recently in the more special sphere

suggested by Captain Marris, we are convinced of its utility as an aid to diagnosis.

The appearance of jaundice after the tenth day is consistent with enteric fever, but not with spirochaetosis. On the other hand, jaundice may appear early in both diseases, which sometimes present closely resembling clinical pictures (e.g. Case IV, Table II). With the diminished frequency of spots in enteric, their absence is of correspondingly diminished significance. To the minds of those who see many cases of pyrexia a palpable spleen suggests enteric (provided malaria can be excluded), because in this disease it is relatively so much more common. If one may judge, however, by this series of enteric jaundices the palpable spleen is becoming less frequent, for it is only present in four out of twenty-six cases. In spirochaetosis it is certainly unusual—only two out of eighteen cases in our series (Table I).

The slowness of the pulse in proportion to the fever is a feature common to both enteric and spirochaetosis. The blood pressure in typhoid and para-typhoid is commonly 100 to 105 (systolic), which is low in comparison with other infections.

Leucopenia cannot be depended on as evidence of enteric. It is probably only present at the beginning of the illness, and is not even constant. Note, for instance, Case IV, Table II, in which on the eighth day the white cell count was 23,000.

Herpes labialis is evidence in favour of spirochaetosis, in which, however, it is not always present. Epistaxis may occur in either enteric or spirochaetosis, but haemoptysis, haematemesis, melaena, or purpura are strongly suggestive of spirochaetal infection.

Here again it must be remembered that in the milder cases of the latter this valuable bit of evidence is often absent.

The presence of herpes or haemorrhage in an early stage of any fever would suggest the injection of 5 c.c. of the patient's blood into a guinea-pig, even if jaundice had not appeared, bearing in mind that spirochaetosis exists without jaundice, though how often we do not as yet know. To be effective inoculation of the guinea-pig has to be done before the fifth or sixth day. This limits its application; and further, guinea-pigs are not always available.

The finding of spirochaetes in the urine may be relied upon, though perhaps two or three examinations at intervals may be necessary. An effective method is to draw off 20 c.c. from the lower stratum of a urine which has been standing, spin for ten minutes, pour off the top fluid, replace it with distilled water, shake and spin again; repeat the process; then make smears from the final deposit and stain with Fontana. Plate 15, B, shows a variety of spirochaetes from one of these urines. To avoid error Lieutenant Bedson examined control urines from cases of other diagnosed fevers. In one case he found spirochaetes, shown in Plate 16, A, which are morphologically distinguishable from the specific spirochaete under discussion; they are broader and have a distinctive and constant shape.

Reverting to enteric jaundice, the bacteriological findings call for some

comment. It is to be noted how comparatively seldom the organisms are found, viz. in seven out of twenty-six cases. If the patients had been triply inoculated this would perhaps be in accordance with expectations, for the modified infection would be likely to discharge fewer bacilli into the urinary and intestinal tracts.

But of the nineteen cases of paratyphoid A and B, only two had been so inoculated, and yet the organism was only found in seven cases. Apart from inoculation it may be because the infection is milder.[12]

Under such circumstances the bacteriological diagnosis has to be based on the variations of the agglutinations on three or four occasions, separated by periods of four or more days.

There is no doubt that the reliability of agglutination has been greatly enhanced by the technique of Professor Dreyer, and that as a means of diagnosis its value is great. Where the variations in the agglutinations are marked—say, for example, 1,200, 3,675, 2,822–1,534 in typhosus—surely no one would doubt the conclusion.

Where such variations of reading are less marked, and especially if the agglutinations in the paratyphoid members of the family simultaneously show disturbance, correct inference is more difficult.

On what degree of variation can a positive diagnosis be based ? The answer to this question is the more important where the clinical manifestations are ill-defined or anomalous. Out of this another question arises. In patients who have been inoculated against enteric, do other fevers affect the agglutination curves ? Further work is needed before a final answer to this question can be given. The importance of it is illustrated by the following case : The patient was suddenly seized with generalized pains, prostration, and headache. The temperature was 102°–103° for two to three days, and on the fifth day he became jaundiced and rather drowsy. About the fourth or fifth day herpes on the lips appeared.

On the tenth day the patient was still apathetic and very yellow; there was a diffuse purplish macular rash all over the chest and abdomen; the liver was enlarged and the edge of the spleen was just palpable; the temperature was subnormal, and the pulse-rate was 96. Thereafter the symptoms abated, and the patient gradually recovered.

On the sixth day of illness a guinea-pig was inoculated with the patient's blood, but did not develop jaundice. Spirochaetes were found in the urine on the eleventh day, and in abundance.

The following figures show the result of the agglutinations to paratyphoid A in this case :

Date.				Agglutinations to A.
27. 8. 16	.	.	.	160
1. 9. 16	.	.	.	1,300
8. 9. 16	.	.	.	640
13. 9. 16	.	.	.	600

[12] Most of the cases of typhoid and paratyphoid fevers now occurring in the Expeditionary Force are so mild as to present a clinical picture notably dissimilar from that usually associated with the term Enteric Fever.

On the agglutination curve the Bacteriological Department reported that the patient was suffering from paratyphoid A fever.

The question arises as to which infection was the cause of the patient's illness. Clinically, the case had more the appearance of spirochaetal than of enteric jaundice. The typical spirochaetes were demonstrated in the urine. Was it a case of mixed infection or were the agglutinations being influenced by the spirochaetal infection?

Considering that these varieties of jaundice might be due to a duodenitis, attempts were made to obtain organisms directly from the duodenum, by means of intubation with an Einhorn's tube. The perforated metal capsule and attached tube were sterilized and filled with sterile water; the capsule was then coated with a thin layer of specially prepared fat which would only dissolve in alkaline duodenal juice.[13] In this way contamination while swallowing is prevented. It is necessary that the patient's stomach should be empty at the time of the intubation. After an interval of fifteen to thirty minutes an alkaline bilious fluid can be sucked up by a syringe, or siphoned off. If there is delay, the fatty covering of the capsule can be blown off by pressure from a syringe attached to the tube. The fluid so obtained is used for investigation.

In this way many cases of spirochaetal and enteric jaundice have been examined.

In no case has an organism bearing the peculiar characteristics of *Bacillus typhosus, paratyphosus A* or *B*, been obtained by this method. However, various coliform organisms have been isolated, and occasionally also staphylo-cocci and streptococci.

Samples of duodenal contents withdrawn from patients suffering from spirochaetal jaundice have on numerous occasions shown the presence of polymorphonuclear leucocytes and large mononuclear cells. These cells were obviously the result of local inflammation.

With regard to the types of jaundice here described, a correct diagnosis can usually be arrived at by a consideration of all the data, though some of the cases, and especially the milder ones, do present difficulties.

It is a great pleasure to acknowledge the help which we have obtained from others in the investigation of our cases.

The bacteriological work has been done by the staff of the 14th Stationary Hospital under the directorship of Lieut.-Col. Gratton, R.A.M.C., and now under Capt. Perry, R.A.M.C., by Lieut. Bedson, R.A.M.C., and by Major Carmalt-Jones, R.A.M.C. Dr. C. H. Browning has been generous with his knowledge. For the specimens and drawings of spirochaetes we are indebted to Lieut. Bedson. The coloured illustrations are a high tribute to the skill of Mr. Shiells and Mr. Ford.

[13] Prepared by Mr. H. Hurlstone, Ph.C., of Bell and Croyden.

APPENDIX.

A case which has come under observation too recently to be incorporated in the text is of sufficient importance to be briefly described here.

The illness began suddenly with head and body pains, weakness, and chilliness. On the second and third days there was repeated vomiting. On the first three days the temperature varied between 102·4° and 100·2°. On the third day herpes appeared round the mouth and jaundice was noticed; on the fourth day the temperature fell to normal and the jaundice rapidly deepened. On the fifth day there was coffee grounds vomiting, the urine contained much albumin and epithelial and erythrocytic casts, but no spirochaetes. The patient had become very ill with a dark brown tongue, and had a tonic convulsion during which he became pale and almost pulseless. On the subsequent days epistaxis, haematemesis, melaena, and purpura occurred, and death ensued from toxaemia and anaemia on the twelfth day. There was no return of fever after the temperature fell on the fourth day. Early in the illness the stools contained bile; later they were clay-coloured or black, due to altered blood.

The blood pictures were as follows:

On the 8th day : Red cells 4,480,000
White cells 12,000
Differential count : Polymorphonuclears . 64·3 per cent.
Lymphocytes . . . . . 28·1 per cent.
Mononuclears . . . . 3·7 per cent.
Eosinophils . . . . . 0·9 per cent.
No nucleated reds or poikilocytes.
No polychromasia.
On the 12th day : Red cells 1,815,000
White cells 32,000
Differential count : Polymorphonuclears . 97·3 per cent.
Lymphocytes . . . . . 1·8 per cent.
Mononuclears . . . . . 0 per cent.
Eosinophils . . . . . 0·9 per cent.
No nucleated reds.
Some poikilocytes.
Some polychromasia.

The urine contained the characteristic spirochaetes on the twelfth day, but none at the first examination on the sixth day.

A guinea-pig was inoculated with 5 c.c. of urine on the seventh day, but with negative results. The agglutinations were negative to enteric fever.

At the autopsy the appearances were identical with those described in Cases II and IV. The stomach and small intestine contained much blood of gastro-duodenal origin. The stomach and duodenum were accurately pictured by Plate 10, and the common bile duct when opened by Plate II. The last half-inch of the duct was swollen and of bluish colour, in resemblance to the duodenum and in contrast to the rest of the duct. Before the common bile duct was opened a probe passed into the duodenum dislodged a formed plug which was impacted in the ampulla. A film made from this plug showed numerous epithelial cell nuclei embedded in a matrix of mucin. The appearances suggested an obstructed papilla, and such obstruction would be favoured by the epithelial folds within the ampulla (Plate 14).

The liver was normal in size, yellowish green, and slightly friable; its lobular pattern was distinct: a film made from a scraping showed one characteristic spirochaete.

The gall-bladder was of normal size and contained very viscid bile. The kidneys showed marked changes; the pattern was blurred and the cortex was swollen, and showed yellow opaque alternating with dark brown areas. Cultures taken from the gall-bladder and spleen were negative to enteric fever.

The minute anatomy of the liver resembled that of the early cases, as illustrated in Plate 13. Thus, there was no striking alteration in the trabecular arrangement of the cells and variations in the size of the nuclei were not marked; mitoses were scanty. On the other hand, there was clear evidence of bile stasis, as already described. Large clear vacuoles were seen in a number of liver cells near the centres of lobules; but staining with Sudan III did not show the presence of fat anywhere. In one place a hepatic venule was seen to be filled with a mass of dissociated liver cells mingled with red blood corpuscles.

TABLE I

No.	History.	Condition on Admission.	Jaundice.	Abdominal Tenderness.	Liver.	
I.	Nov. 10. Faint and drowsy. Vomited Nov. 12. Bile in urine (water like blood) Nov. 13. Reported sick	Nov.15. Bowels not opened 7 days. Distension of abdomen. Very drowsy and ill. Very furred tongue	Marked universal	Epigastric distension lessened by enema.	2 fingers' breadth below costal margin	
II.	Dec. 16. Sudden chill. Headache. Fever pains in thigh. Nausea	Dec. 24. Round worm from stomach. Melaena. Vomiting and nausea marked Dec. 29. Asthenia and convulsions. Death	Marked universal	Epigastric pain	3 fingers' breadth	
III.	Dec. 10. Ill for 9 days. Diarrhoea and vomiting. Dec. 12. Reported sick. Pains in legs and haematemesis Dec. 19. Jaundice	Dec. 26. Dyspnoeic. Great abdominal distension	Marked universal	Considerable	3 fingers' breadth	
IV.	Nov. 3. Pains in small of back and chest Nov. 13. Sore throat Nov. 14. Suddenly vomited. Very ill and vomiting till 28th	Nov. 28. Jaundice noticed on 5th day. Spasms often across epigastrium. Drowsy. Headache and constipation	Marked universal	Very tender across upper abdomen	2 fingers' breadth	
V.	Dec. 20. Reported sick: incontinence of urine Dec. 25. Jaundice. Shivering and coughing Dec. 26. Epistaxis	Dec. 27. Cough. Sleepless. Headache. Bronchitis	Marked universal	None	3 fingers' breadth	
VI.	Jan. 20. Vomited everything Jan. 22. Reported sick. Jaundiced	Jan. 28. Heartburn. Petechiae on abdomen and legs	Moderate	Some distension. No tenderness	Nil	
VII.	Nov. 19. General pains. Giddiness Nov. 24. Sickness and vomiting Nov. 25. Jaundice. Green vision	Nov. 28. Epistaxis Nov. 29. Drowsy. Haemoptysis. Melaena	Marked universal	Distended and tender	Nil	
VIII.	Nov. 6. Weak and misty eyes. Headache Nov. 13. Reported sick Nov. 16. Jaundice	Nov. 22. Very ill. Cholaemic. Tongue brown fur. Haemoptysis. Crepitations in third left intercostal space	Very intense	Epigastric tenderness	3 fingers' breadth	
IX.	May 10. Pain in head and at back of eyes May 16. Jaundice. Epistaxis	May 23. Dry tongue. Fading jaundice	Fading universal	Epigastric pain	Nil	

TABLE I

Spleen.	Blood.			Urine.			Stools.	Pain in Back and Limbs.	Progress.
	Hb.	R. B. C.	W. B. C.	Bile.	Albu-min.	Casts.			
Nil	100	5,200,000	13,000 P.M.N. = 63 Lymph. = 33 Eosin. = 4	+ +	$\frac{1}{10}$ test-tube	Hya-line and granu-lar	Some bile	Slight	Nov. 27. Gall-bladder opened and drained for 14 days Dec. 18. Jaundice dis-appeared. Dec. 30. England
Nil			34,000 P.M.N. = 93 Large Mono. = 1 Lymph. = 6	+ +	$\frac{1}{10}$ test-tube	Nil	Light yellow	Pains in thighs	Dec. 29. Died
Nil	70	3,000,000	20,000					Nil	Jan. 9. Died
Nil			22,500	+ +	Trace	+ +	Almost clay-coloured	Nil	Dec. 1. Died
Nil			12,400	+ +	$\frac{1}{8}$ test-tube	Granu-lar	Light brown	General pain and tender-ness in thighs and calves	Marked secondary fever lasting 23 days Jan. 29. England
Nil			10,000	+	Nil	Nil		Nil	No secondary fever Feb. 16. England
Nil			12,500	+ +	Trace	Nil	Light brown	Tender calves	No secondary fever Dec. 23. England
Nil		4,600,000	16,500 P.M.N. = 69 Lymph. = 31	+ +	$\frac{1}{8}$ test-tube	+ +	Slate grey	Abdo-men and thighs	Dec. 23. England Secondary fever for 10 days
Nil			11,300 P.M.N. = 81 Lymph. = 15 Eosin. = 4	+	+	Nil		Marked	Secondary fever for 4 days May 31. England

TABLE I (*continued*)

No.	History.	Condition on Admission.	Jaundice.	Abdominal Tenderness.	Liver.
X.	Nov. 21. Sudden vomiting Nov. 24. Vomiting. Haematemesis. Melaena. Jaundice	Nov. 29. Anorexia. Furred tongue	Moderate universal	Cramping pains in upper abdomen	2 fingers' breadth
XI.	Dec. 22. Sudden weakness —had to fall out Dec. 27. Jaundice	Jan. 1. Drowsy. Urticaria. Anorexia. Purpura	Intense	Epigastric tenderness	3 fingers' breadth
XII.	Nov. 28. Pains in legs— fainted Dec. 1. Haematemesis. Jaundice (Dec. 2)	Dec. 4. Pains behind knees. Brown furred tongue	Marked universal	Tenderness of upper abdomen	3 fingers' breadth
XIII.	Feb. 12. Prostration Feb. 15. Jaundice Feb. 20. Haematemesis	Feb. 22. Epistaxis. Anaemia. Loss of flesh	Marked	Slight	3 fingers' breadth
XIV.	May 13. Sudden headache and body pains May 15. Cough and haemoptysis May 19. Jaundice	May 17. Headache. Haemoptysis. Vomiting. Purplish discoloration of skin	Marked universal	Nil	Nil
XV.	Aug. 7. Sudden diarrhoea Aug. 9. T.=101°. Melaena. Marked prostration Aug. 14. Haemoptysis	Aug. 16. Marked jaundice. Basal crepitations. T. = 101·2°. Tongue dry, furred	Well-marked universal. Aug. 26. Fading rapidly. Sept. 1. Almost gone	Marked in right hypochondrium	3 fingers' breadth
XVI.	June 9. Felt seedy June 10. Reported sick. T. = 103°. Pains in legs and weakness June 13. Jaundice	June 16. Marked jaundice. Drowsy. Occasional vomiting. Slight abdominal distension	Well-marked universal	Slight in right hypochondrium	Hand's breadth below costal margin
XVII.	June 15. Sudden pains all over. Headache. Vomiting. T. = 102° June 15–21. Weak. Anorexia. Vomiting June 21. Jaundice	June 24. Jaundiced and drowsy. Feeling miserable. Tongue dry, brown fur	General marked	Slight across epigastrium	3 fingers' breadth
XVIII.	July 9. Sudden vomiting and prostration. T. = 103° July 9–16. Prostration. Vomiting. Photophobia. July 16. Jaundice	July 20. Drowsy. Bronchitis. Haemoptysis. Dyspnoea.	General marked	Upper abdomen very tender	3 fingers' breadth

TABLE I (*continued*)

Spleen.	Blood.			Urine.			Stools.	Pain in Back and Limbs.	Progress.
	Hb.	R. B. C.	W. B. C.	Bile.	Albu-min.	Casts.			
Dullness to rib margin			10,000	+	Trace	Nil	Slate grey	Pains abdomen and thighs. Paraes-thesia left foot	No secondary fever Dec. 25. England
Nil			20,000	+ +	+	Hya-line and granu-lar	Yellow brown	Nil	Auricular fibrillation
Nil			5,000	+ +	Trace	Granu-lar	Yellow brown	Very marked in legs	
Nil	40	2,160,000	22,000 P.M.N. = 67 Lymph. = 35 Large Monos. = 5 Eosin. = 3	+	Trace	Nil		Pains in legs	March 6. England
Nil	75	4,400,000	13,000	+ +	⅛ test-tube	Granu-lar	Pale mucoid	Consider-able	
Not palpable	80	4,860,000	24,000	+ +			Bile-coloured blood (2)	Present	Spirochaetes found in the urine Aug. 21. England
Not felt			13,000 P.M.N. = 82 Lymph. = 10 Large Monos. = 5 Eosin. = 2	+ +	Trace		Light yellow brown	Marked	Spirochaetes found in the urine June 22. England
Not felt			11,500 P.M.N. = 73 Lymph. = 23 Eosin. = 4	+ +	None	None	Light yellow brown	Marked	Spirochaetes found in the urine June 28. England
Not felt			9,700 P.M.N. = 75 Lymph. = 18 Large Monos. = 7	+ +	Trace	Few	Light brown	Slight	Spirochaetes found in the urine July 24. England

TABLE II

No.	Onset of Illness.	On Admission.	Jaundice.	Liver.
I.	Mar. 31. Sudden abdominal pain. Vomited	Apr. 8. Jaundice. Drowsy and ill	Marked (8th day)	3 fingers' breadth
II.	Sept. 23. Sudden headache. Giddiness. Weakness	Sept. 31. Heavy; flushed. Slight jaundice	Slight (8th day)	Nil
III.	Oct. 23. Sudden headache. Pains in lower legs. Nov. 2. Frequent vomiting. Jaundice	Nov. 8. 'Rather ill.' T. = 98°	Jaundice (10th day)	Nil
IV.	Aug. 27. Sudden headache. Prostration. Aug. 28. T. = 103·6°	Aug. 30. Vomiting. Icterus	4th day	3 fingers' breadth
V.	Jan. 30. Sudden shivering. Anorexia. Feb. 1. Jaundice	Feb. 2. Very toxic. Upper abdomen tender	Very marked (2nd day)	3 fingers' breadth
VI.	Apr. 16. Sudden general pains. Apr. 20. Early vomiting. Yellow	Apr. 22. Drowsy	Very marked (4th day)	3 fingers' breadth
VII.	Aug. 1. Sudden headache and vomiting	Aug. 8. Jaundice	6th–7th day	?
VIII.	Apr. 23. Sudden pains in legs. Vomited. Apr. 26. Jaundice	Apr. 30. Heavy. T. = 101°	Very marked (4th day)	3 fingers' breadth
IX.	Oct. 19. Gradual abdominal pain. Vomited. Few days later jaundice	Oct. 29. Indefinite malaise	Faint (early)	Tenderness only
X.	May 20. Acute general pains. T. = 102°. No spots	May 26. Headache. Cyanosis	6th day	Nil
XI.	Feb. 24. Gradual seediness. Headache. Vomiting. Feb. 28. Jaundice	Mar. 3. T. = 103°. Headache. No jaundice noted. Nausea	Few days only at outset	Tenderness
XII.	May 3. Sudden pain in abdomen. May 4. Headache. General pains	May 13. Jaundice. Epistaxis	7th day–9th day, disappearing	Not mentioned
XIII.	Feb. 14. Gradual giddiness. Shivering. Epistaxis. Feb. 22. Slight jaundice	Mar. 3. Slight jaundice. No spots	8th day, slight	Not mentioned
XIV.	Aug. 20. Sudden headache. No other pain. No vomiting. No diarrhoea	Aug. 24. Bronchitis. Aug. 26. Jaundice	6th day, moderate	Nil

TABLE II

Spleen.	Inoculation.	Bacteriology.*	Progress and Remarks.
Much enlarged	Feb./15. T. V.† + 2	(6) Falling titre in T.	Duration of illness 33 days
Nil	Oct./14. T. V. + 2	(4) Falling titre in T.	Duration of illness 43 days. Fever of relapse, 15th–23rd days
Nil	Feb./15. T. V. + 2	(4) Variable titre in T.	Duration of illness 44 days
Nil till 15th day, then palpable	May/15. T. V. + 2	(3) Rising titre in T., up to 1 in 3,125	
Palpable	Aug./15. T. V. + 2	(7) Very variable titre in A	Duration of illness 60 days. Fever of relapse, 10th–26th days
Nil	June/15. T. V. + 2	(3) Variable titre in A. Blood culture A	Duration of illness 25 days
?	Dec./14. T. V. + 2 May/16. $\frac{T. A. B.†}{2}$	(4) Rising titre in A	
Not mentioned	Sept./14. T. V. + 2	(4) High and variable titre in B. Blood culture B	Duration of illness 61 days
Nil	Nov./14. T. V. + 2	(3) Small titre in B. 1 in 25; 1 in 80 ?	Duration of illness 28 days
Nil	T. V. + 7. 3.4.16. T. A. B.	(4) Variable titre in B	Duration of illness 48 days. Fever of relapse, 24th–33rd days
Nil	T. V. + 2. Aug./14 and June/15	(4) Variable titre in B	Duration of illness 37 days
Nil	Sept./15. T. V. + 2	(3) Variable titre in B	Duration of illness 51 days. Fever of relapse, 27th–33rd days (very slight)
Nil	Sept. and Oct./14. T. V. + 2	(4) Aggl. 1 in 20 in B	Duration of illness 37 days
Nil	... ...	... ...	Duration of illness 23 days. At commencement was picture of bronchitis and jaundice

* In the column Bacteriology the left-hand numerals indicate the number of agglutinations observed.   † T. V. = Typhoid.   T. A. B. = Typhoid and paratyphoid A and B.

TABLE III

No.	Onset of Illness.	On Admission.	Jaundice.	Liver.
I.	July 10. Gradual onset with tonsillitis	July 27. Recently yellow	17th day or previously	Enlarged
II.	Jan. 2. Sudden colic. Diarrhoea. Few small spots	Jan. 20. Drowsy	18th day	Tender—gall-bladder
III.	Sept. 22. Gradual onset with diarrhoea (5 days). Headache. Temperature and abdominal pain	Oct. 3 (19th day). Temperature normal	Moderate noticed 12th day	Nil
IV.	Mar. 1–7. Gradual headache. Fever. Diarrhoea. One typical spot	Mar. 26 (20th day). 3 spots on abdomen	Apr. 1 (26th day) first noticed	Gall-bladder
V.	Mar. 17. Gradual pain in left side. Constipated. Headache. T. = 101·2°. Vomited	Apr. 1. Tongue thick fur. No spleen enlargement. Frontal pain	Apr. 18 (31st day) till Apr. 25	Nil
VI.	Oct. 12. Gradual headache. Lassitude	Oct. 25. T. = 102·8°. Drowsy and ill	21st–25th days slight, with pyrexia	Not mentioned
VII.	Oct. 20. Gradual headache. Weakness and constipation. Several large spots	Nov. 10. Sallow. Slight jaundice	21st day	Not mentioned
VIII.	Aug. 27. Gradual headache. General pains. Epistaxis	Sept. 7. Jaundice	11th day	Nil
IX.	No history on notes. Gradual ?	Apr. 29. Admitted very ill. T. = 101°. P. = 130. Acute pneumonia	May 3 slight	?
X.	Aug. 5. Gradual headache. Lassitude. Able to work for 3 weeks	Aug. 22. Admitted for a burn Aug. 26. Jaundice and mild pyrexia for 3 following weeks	21st day moderate	Nil
XI.	June 5. Sudden headache. Vomiting June 22. Slight jaundice. Large number of spots	June 22. No physical signs, except jaundice	17th day	Nil
XII.	May 3. Sudden vomiting. Faints. Headache. No spots	May 10. Drowsy	19th day slight	Nil

TABLE III

Spleen.	Inoculation.	Bacteriology.*	Progress and Remarks.
Nil	27 July/15. T. A. B.	(4) Varying titre in T.	Duration of illness 19 days
Nil	... ...	Jan. 31. T. from stool	Duration of illness 40 days
Palpable	Feb./15. T. V. + 2	(2) Aggl. 1 in 2,550 A.	Duration of illness 40 days. Fever of relapse, 15th–26th days
Enlarged ?	... ...	Mar. 31. B from stool. Titre + in B	Duration of illness 65 days. Relapse of fever for 5 days
Nil	Oct./14. T. V. + 2	(4) Falling titre in B	21st–28th days, small relapse, with jaundice
Nil	Feb./15. T. V. + 2	Nov. 7. B from stool	Duration of illness 63 days. Fever of relapse, 33rd–39th days
Nil	June/15. T. V. + 1	Nov. 13. B from stool Dec. 4. B from urine	Duration of illness 69 days
Nil	Jan./15. T. V. + 2	(4) Falling titre in B	Duration of illness 56 days
Nil	Mar./15. T. V. + 1	Apr. 16. B from urine	May 4, died
Nil	T. V. + 2	Sept. 5. Aggl. B 1 in 50	Convalescent (Sept. 15)
Nil	Oct./14. T. V. + 2	June 30. B from stool July 7. A from blood	Duration of illness 89 days. Fever of relapse, 57th–69th days
Tender	June/15. T. V. + 2 Dec./15. T. V. + 1 12 Apr./16. T. A. B. + 1	(4) Varying titre in T. A and B Diagn. = Enteric group	Duration of illness 61 days. Fever of relapse, 14th–29th days

* In the column Bacteriology the left-hand numerals indicate the number of agglutinations observed.

DESCRIPTION OF PLATES.

PLATE 10.   The stomach and duodenum from a case of spirochaetal jaundice, showing the oedematous and congested mucous membrane and the papilla.

PLATE 11.   A portion of the duodenum from a case of spirochaetal jaundice.

PLATE 12.   Naked-eye appearance of the liver in a case of spirochaetal jaundice.

PLATE 13.   Sections of liver from a case of spirochaetal jaundice.

PLATE 14.   A. Section across the ampulla of Vater, showing the numerous folds, recesses, and crypts in the mucous membrane lining the ampulla.   B. Enlargement of part of the section shown in A.

PLATE 15.   A. Guinea-pig's liver, showing spirochaetes.   B. Field showing spirochaetes and cocci in urine.
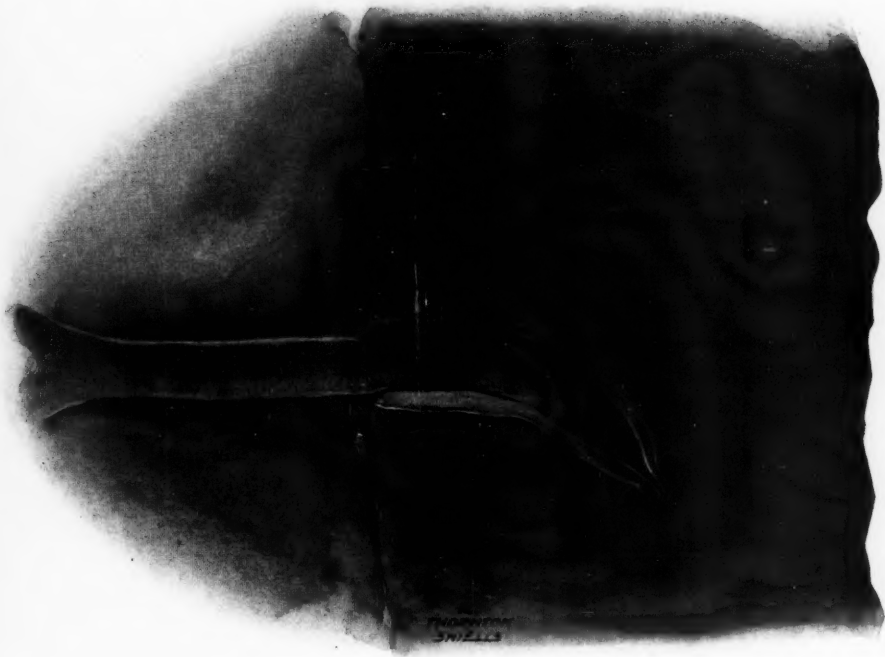
PLATE 16.   A. Control urine showing spirochaetes, other organisms, and crystals. B. Sections of liver from case of spirochaetal jaundice (dead in a fortnight).

The Stomach and Duodenum from a case of Spirochaetal Jaundice, showing
the oedematous and congested mucous membrane and the papilla.
The common bile duct shows no change.
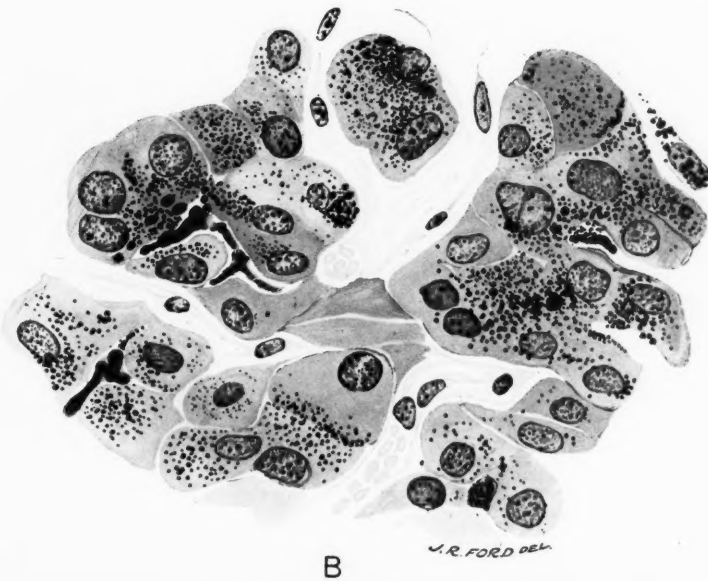The neighbouring glands are enlarged.

A portion of the Duodenum from a case of Spirochaetal Jaundice.
The terminal portion of the bile duct is swollen and congested,
especially round the papilla.
The rest of the common bile duct is normal in appearance.

Naked-eye appearance of the Liver in a case of Spirochaetal Jaundice.

A

B
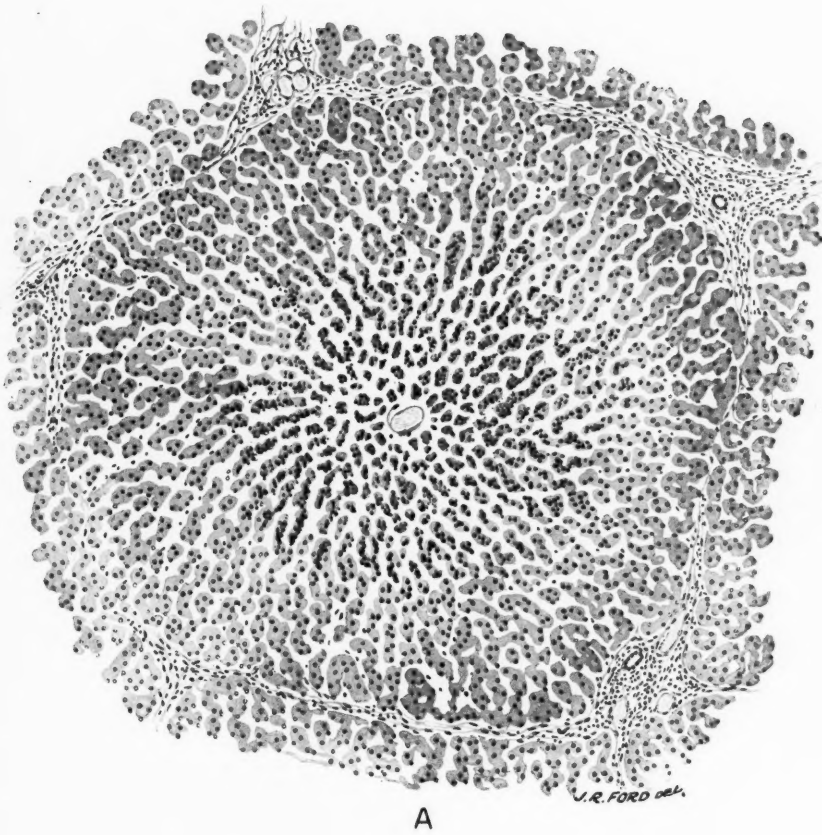
Sections of Liver from a case of Spirochaetal Jaundice. The Liver
cells and their arrangement appear normal.
A shows collections of cells in portal areas.
B shows biliary stasis.

A Section across the ampulla of Vater showing the numerous folds, recesses, and crypts in the mucous membrane lining the ampulla.

    (a) Ampulla.
    (b) Duodenal mucous membrane.
    (c) Crypts.
    (d) Submucous coat.
    (e) Muscular coat of duodenum.
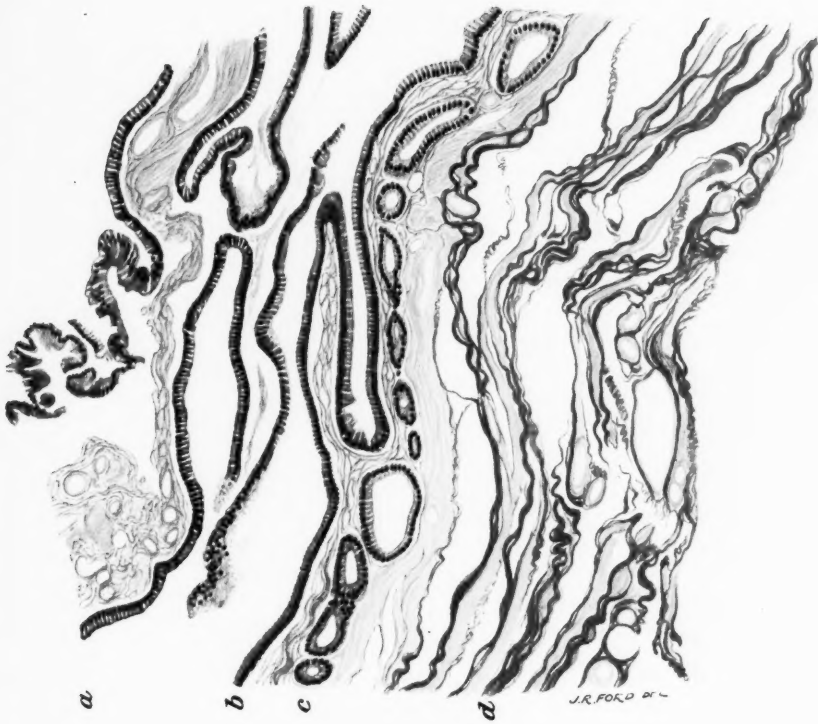
B Enlargement of part of the section shown in A.

    (a) Folds within lumen of ampulla.
    (b) Mucous membrane of ampulla.
    (c) Crypts.
    (d) Submucous coat.

A Guinea-pig's Liver showing Spirochaetes.

B Field showing Spirochaetes and Cocci in urine.

(A)   Control urine showing Spirochaetes, other organisms and crystals

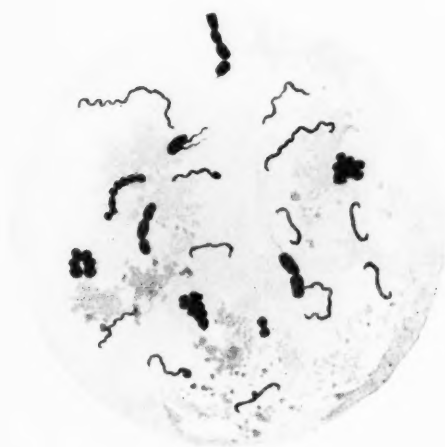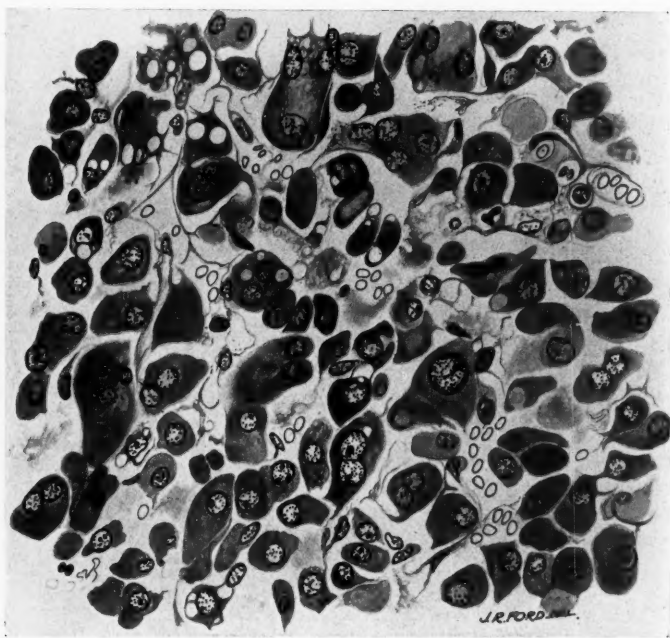(B)   Section of liver from case of spirochaetal jaundice. (Dead in a fortnight)

LIPODYSTROPHIA PROGRESSIVA

By F. PARKES WEBER

LIPODYSTROPHIA progressiva is a rare disease or morbid condition, possibly confined to the female sex, and characterized by the progressive disappearance of the subcutaneous fat from the parts above the lower extremities, that is to say, above the buttocks and the inguinal folds. The term lipodystrophia progressiva was introduced by A. Simons (1911), and the appearance in his case as portrayed in his and E. Holländer's illustrations (1910) may be accepted as altogether typical for the disease (1). Though Simons was undoubtedly the first to use the term lipodystrophia (from the Greek words λίπος, δυς-, and τροφή, signifying respectively *fat*, *badly*, and *nourishment*), a characteristic example of the disease was shown by Harry Campbell in 1907, at the Clinical Society of London, under the heading ' Disappearance, more or less complete, of the subcutaneous fat above the region of the lower extremities ' (2).

The fat atrophy seems first to attract attention in the face, and later on to spread to the trunk and upper extremities. Perhaps in some cases it remains limited to the face and neck, or face, neck, and thorax ; in Lewandowsky's case, referred to farther on, the disease, although it had already lasted two years, had not yet affected the upper extremities. Though the disease is called *progressive* lipodystrophia, it is really not progressive in all senses of the word, for the lower extremities and the buttocks are never involved ; in most (nearly all) cases, indeed, there seems to be an abnormal accumulation of subcutaneous fat in the thighs and gluteal regions (rarely in the lower abdomen also), such as occurs in many females, especially at middle age.[1] Moreover, when the subcutaneous fat has nearly all disappeared from the affected regions, the disease comes to a standstill. Although at the commencement there may have been associated neurotic or other troubles, when the disease once comes to a standstill, and sometimes during the progress of the disease, the general health appears to be in no wise affected by the lipodystrophia. The patients are ordinarily able to do as much work and stand as much fatigue as the average of normal women of the same age, or they may even excel in energy and strength. A cause of annoyance and trouble may be that employers and others, owing to the wasted appearance of the face, may suspect the presence of a disease of evil repute, such as pulmonary tuberculosis or cancer.

The aetiology of the disease is unknown, but an endocrinic origin has been suspected, that is to say, the peculiar fat atrophy in question has been supposed

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[1] In females the predominance of subcutaneous fat about the thighs and gluteal regions is practically a secondary sex-character. The gluteal prominence is greatly exaggerated in some African races, constituting the racial peculiarity known as ' steatopygia ', which is illustrated by the pictures of the ' Hottentot Venus '.

to be a result of some disorder of the internal secretions, possibly (if the disease turns out to be really limited to the female sex) in some way connected with the female sexual apparatus. However, menstruation and the ordinary sexual functions appear to be unaffected. Feer (13) suggests disorder in the function of the thyroid gland. Thyroid treatment and various drugs and other methods of treatment have been tried, but without any satisfactory result.

It is possible that the disease occurs relatively more frequently in women of Hebrew race than in others. In my first case the patient was of Hebrew parentage, and so were Harry Campbell's and Herrman's patients. Several other patients, however, were certainly not Hebrew. If, moreover, the disease is slightly less rare amongst those of Hebrew origin than amongst others, it must nevertheless be exceedingly rare. During the whole time (more than twenty years) of my work as physician to the German Hospital in London (the in-patients and out-patients of which are largely Jews from Russia, Russian Poland, Germany, Austria, and the Balkan States) I have not met with a single case at that hospital, nor have I heard that any of my colleagues at the hospital have come across one.

In regard to the age at which the disease commences, and the circumstances (if any) which the patient or her friends suppose to have acted as exciting causes, there seems to be considerable difference in different cases; but the disease is one of the first half of life and generally commences in childhood, before puberty, especially at the age of six years or thereabouts.

In a case on which I published a note in 1911 (3), the patient, who was an unmarried woman, aged 27 years, of Hebrew parentage, presented no evidence of any visceral disease. She was said to have been a healthy girl up to the age of 16 years, when menstruation commenced. Since then she had had various troubles, and had likewise been treated for dyspepsia and insomnia. But it is doubtful whether these troubles had anything to do with the lipodystrophia. She was active and discontented with life in her parents' home, being desirous of obtaining some useful occupation, which would render her more independent.

Since then I have met with another case, in a somewhat older woman, who, apart from the fat atrophy in question, enjoys apparently perfect health. Mentally she is also normal, but does not like people thinking that owing to the emaciated aspect of her face she must have 'consumption'. She is quite certain that the fat atrophy commenced after an attack of measles, at 7 years of age, but it has long ago reached its maximum and is now quite non-progressive.

In Harry Campbell's case (4), when he first demonstrated it (1907), the patient was 21 years old. Dr. Campbell kindly informs me that she is of Hebrew parentage. The fat atrophy commenced at the age of 6 years and gradually progressed during the next eight years or so. The face was the part first affected. Dr. Campbell tells me that cosmetically she has been greatly improved by paraffin injections into the subcutaneous tissues of the face, for the first time in 1914, and again about one year later (as the paraffin had apparently become gradually absorbed after the first injection).

The patient of Simons and Holländer (5) was 21 years old when her case was described in 1910. The fat atrophy was first noticed in the face, when she was 11 years old, and then gradually spread over the trunk and upper extremities. The leanness of the face, however, seems to have been preceded by excessive accumulation of fat in the gluteal region, for an increase in the size of that part of the body had attracted her mother's attention when she was only 5 years old. The appearance of her face was of special importance to her, as she was a professional dancer, and from the cosmetic point of view Holländer obtained a temporary good result by injecting a sterilized mixture of human fat and mutton suet into the subcutaneous tissue of her face. The good result, however, did not last long, for absorption soon took place. A 'biopsy' examination of the affected skin and subcutaneous tissue was made in this case, and (unlike what is found at post-mortem examinations on even the most emaciated subjects of pulmonary tuberculosis) practically complete absence of fat was noted, so that only traces could be demonstrated by careful microscopical examination (6).

In a case which Sir William Osler kindly gave me permission to mention (7), and which doubtless belongs to the same class, the leanness was first noticed when the patient was about 5 years old, the face and back being the earliest parts to be affected. In 1895, when Sir William Osler saw her, the contrast was very great between the extreme thinness of the face, trunk, and upper extremities, and the plumpness of the parts below the hips. Menstruation commenced at 12 years of age. In February, 1913, information was obtained that, though this patient still looked thin and weak, she said that she felt well and was actually stronger than most ordinary women.

A case, evidently of the same class, was described by A. Pic and Ch. Gardère at the Society of the Medical Sciences of Lyon on December 23, 1908, as an example of 'generalized atrophy of the face and parts of the body above the umbilicus with pseudo-hypertrophy of the pelvic region and lower extremities' (8). The patient was a woman (age not stated) whose illness had commenced four years previously, with sudden loss of weight and strength, anorexia, digestive troubles, and pallor. There was no cough. She was unable to continue her work, as the slightest effort gave rise to palpitation of the heart and feeling of oppression. She was also mentally depressed, and gave way to frequent attacks of crying without any reason. After a 'rest and feeding cure' she commenced to regain strength, the lower extremities increased in size, and her pallor disappeared. At last, after an interruption of one and a half years, she was able to start work again. Nevertheless, her face, upper extremities, and thorax remained emaciated, whilst her lower extremities progressively increased, chiefly in amount of subcutaneous tissue, so that their size came to be in striking contrast to the skeleton-like appearance of her face and the upper part of her body, in which, however, the mammae retained their normal size. The tendon reflexes in both lower and upper extremities were markedly exaggerated; in the lower extremities, more than one jerk was sometimes obtained by a single tap

('clonic or trepidation type' of response); the plantar reflexes were of the normal flexor type; no disorder of sensation was present. Electrical examination of the muscles showed nothing abnormal. Her gait was natural, and there was no longer any special tendency to fatigue on exercise. Some physical signs in the chest pointed to the presence of slight pulmonary tuberculosis. Menstruation (which had commenced at the age of 15 years) was regular, and had always been so, excepting at the commencement of her illness four years previously, when she had amenorrhoea for six months.

The case of 'segmentary adiposis of the lower limbs' recently published by Laignel-Lavastine and Viard (9) must probably be regarded as belonging to the group we are now considering, though the emaciation of the face and upper part of the body was less decided. Their patient was an unmarried woman, aged 39 years, an embroiderer, who complained of great enlargement of the lower extremities. This commenced, according to the patient's account, at the age of 22 years, and first involved the legs, then the thighs, and lastly the buttocks. Various methods of treatment had been resorted to (thyroid extract and iodine, milk diet, &c.), but without satisfactory results. The great size of her lower extremities offered a striking contrast to her thin chest and the general slenderness of the upper part of her body. The left thigh was decidedly larger than the right thigh, but both thighs, both buttocks, and both legs shared in the enlargement. The mammae were very small. The thyroid gland was slightly enlarged. The menstrual periods, which had commenced at 14 years of age, lasted only two days each time. At the Salpêtrière the patient had been given thyroid and ovarian extracts, but as yet without any effect on the size of the lower extremities.

Laignel-Lavastine and Viard, besides the case of Pic and Gardère already described, quote a case published by L. Barraquer, at Barcelona, in 1906. A young woman, aged 25 years, in her thirteenth year, after an attack of 'influenza', had commenced to waste rapidly in her face and the upper part of the chest. These wasted parts contrasted strikingly with the plump condition of the rest of her body.

In May, 1915, Dr. John Fawcett kindly showed me a typical case of lipodystrophia progressiva in Guy's Hospital. The patient was a young English woman (not of Hebrew origin), aged about 19 years, with apparently nothing abnormal about her, physically or mentally, excepting the fat atrophy. The subcutaneous fat of the whole body down to the pelvic bones was involved in the atrophy. The lower extremities showed a plentiful, but apparently not excessive, covering of fat. The disease had been long quiescent, for it commenced at about $8\frac{1}{2}$ years of age and took only a year or so to reach its present stage. Menstruation, which commenced at $13\frac{1}{2}$ years, was normal.

On May 26, 1913, Toby Cohn (10) demonstrated a typical case of the disease before the Berlin Society for Psychiatry and Nervous Diseases. The patient was 17 years old, and the fat atrophy had commenced when she was 6 years old. The fat atrophy affected the usual parts (down to the region of the pelvic bones).

Recently a great increase in size of the lower extremities and gluteal regions had been noted. The patient likewise complained of weakness in the arms, of frequently feeling cold, and of an abnormal tendency to sweat. Menstruation was normal. The patient's father had had syphilis, but her own Wassermann reaction was negative.

In the discussion (11) on Toby Cohn's paper, Lewandowsky referred to the case of a young woman then under his care, in whom the disease had existed for two years, and, though the face and trunk were affected, the arms as yet had preserved their normal subcutaneous fat; the gluteal region was, as in most cases, overloaded with fat. A. Simons, in the same discussion, mentioned that he had heard that H. Curschmann had seen three cases and that Otfried Förster had seen one case of obvious lipodystrophia progressiva.

Charles Herrman's (New York) case (12) was that of a married woman, aged 32 years, of Hebrew race (from Russia), the mother of children. The fat atrophy in her face had been first noted at the age of 6 years. It commenced insidiously, without fever, pain, or any discomfort. By the age of 11 years (when she came from Russia to the United States of America) the subcutaneous fat of the face had almost entirely disappeared. Later on the lipodystrophia spread to the neck, thorax, and arms. Menstruation commenced at 13 years of age, and she married at 22 years. After that she began to put on fat in her lower parts. Except for the disfiguring appearance of her face she had not suffered in any way from the lipodystrophia. Herrman, in his report of this case, incidentally mentioned that he had seen other examples of the disease, but before he had come across any general account of the subject.

E. Feer, of Zürich, has recently described and illustrated two fresh cases of lipodystrophia progressiva (13). The patients were girls, aged 12 and 10 years respectively (1914), in whom the fat atrophy began at about 6 years of age in the face, spreading gradually to the neck, thorax, and arms. The increase of fat in the thighs and buttocks was more striking in the second case (that of Dr. Boissonnas, of Geneva), in which there was likewise abnormal obesity of the abdominal wall.

E. Jolowicz (1915) has described another case (14). The patient is a single woman, aged 21 years, with nothing special in her family history. In her eighth year it was noticed that her face began to get thinner. The fat atrophy progressed gradually to the thorax and arms, and in the course of a few years reached its present extent. Simultaneously with the fat atrophy in the upper part of the body there was an increase of subcutaneous fat in the buttocks and thighs. At 9 years of age there seems to have been a temporary arrest in mental development, but at present her mental condition is normal. Menstruation commenced at the age of 14 years, and has continued since then. She has had various illnesses, which, however, do not appear to be connected with the lipodystrophia.

Another case is described by Viggo Christiansen (15), that of a girl, 18 years old, in whom there is, as there is in most of these cases, an excess of subcutaneous

fat over the buttocks and lower extremities, contrasting with the want of subcutaneous fat in the face, trunk, and upper extremities. Temporary improvement in the appearance of the face was obtained by paraffin injections. The disease was first noticed when the patient was 12 years old.

Lipodystrophia progressiva seems not to be so rare a condition as was at first supposed. In this paper I have alluded to some twenty cases, and I have heard privately of at least one more. No one can therefore any longer doubt the real existence of the disease or morbid condition in question. In a series of cases, however, the typical ones probably merge into a condition which is relatively quite common in women—namely, thinness of the upper part of the body and relative excess of fat in the lower extremities.

As already stated, nothing certain is known as to the aetiology, and no remedy has been discovered for the fat atrophy. Even cosmetic treatment (paraffin injections, &c.) seems to give only temporary results.

In regard to differential diagnosis I will merely refer to another class of bilateral atrophy of the subcutaneous tissues of the face, which has probably been more frequently noted in males than females, namely the series of cases supposed to be allied to progressive facial hemiatrophy, in fact thought to be (if the expression be permitted) a progressive ' bilateral facial hemiatrophy '; one side of the face being sometimes affected before the other side, or to a greater extent.

Some of the following examples have been quoted by H. Oppenheim, of Berlin, in his large, well-known text-book, and some may possibly have been real but limited lipodystrophia progressiva.

A. Schlesinger (16) refers to a case of that kind observed by himself, two cases recorded by Moebius, one by Julius Wolff (17), and one by Flashar (18). Schlesinger's case was that of a girl, aged 10 years, in Monti's clinic. The facial atrophy commenced at 4 years of age, a few months after measles. It was not accompanied by neuralgia or any kind of pain, and it was noticed on the left side of the face before the right side was involved. One of Moebius's two patients was a woman, aged 28 years, in whom the bilateral facial atrophy was first observed after she complained of pains following an injury to her right eye. The other of Moebius's patients was a woman, aged 19 years, in whom the bilateral facial atrophy was said to have followed local pains and an attack of pneumonia. Wolff's patient was a woman, aged 24 years, in whom the right side of the face commenced to waste before the left side was involved. Flashar's (and Eulenburg's) case was that of a woman, aged 23 years, in whom progressive bilateral facial atrophy followed a supposed attack of measles (without cutaneous eruption) at about 4 years of age.

A case described by Nicaise (19) does not concern us in regard to the present question, because the facial atrophy (in a woman, aged 24 years), although it was bilateral (as far as it went), affected only a vertical stripe, exactly in the middle line of the face, from the root of the nose to the margin of the hairy scalp.

Bilateral wasting of the subcutaneous tissues of the face has also been

observed in connexion with skin lesions (lupus erythematosus?), and in con-
nexion with ozaena (Okouneff, 1907).

Other cases of bilateral facial atrophy have been recorded in England.
In 1905 H. Batty Shaw (20) demonstrated a boy, aged 10 years, who had
commenced to show bilateral wasting of the subcutaneous tissues of the face
when he was $2\frac{1}{2}$ years old. The boy was brought to the hospital because
his mother feared he might have tuberculosis. A. F. Hertz and W. John-
son (21), in January, 1913, brought forward the case of a young man, aged 26
years, whose face had become progressively thinner during the last two
years, so that his friends thought he must be consumptive. There was no
weakness of the facial muscles, and otherwise he was well developed and strong.
He had had double otorrhoea in childhood. The same authors (22), somewhat
later, met with another case of bilateral atrophy of the face, but in that case
it was associated with wrist-drop from lead palsy. The patient was an Italian
plaster-modeller, aged 38 years. In his book on *Diseases of the Nervous System*,
J. S. Bury has reproduced the photograph of a young lad with bilateral facial
atrophy (23).

Other cases possibly of the same kind of bilateral face atrophy have recently
been described by J. Husler (1914) (24). He gives portraits of two boys, aged
10 and 9 respectively, affected in this way. According to A. Simons (25), indeed,
both Husler's cases are genuine ones of lipodystrophia progressiva, differing from
typical cases only in the sex of the patients. It must, however, be remembered
that typical facial hemiatrophy may commence with wasting apparently limited
to the subcutaneous fat.

This brings me to the microscopical appearances of the skin in typical cases
of lipodystrophia progressiva. As already stated, the only change that was
found from the ' biopsy' examination in Simons's case was practically complete
absence of subcutaneous fat. This result has been confirmed by 'biopsy'
examination in Feer's first case (13). The lean skin of an affected part in that
case showed nothing abnormal, excepting relative absence of subcutaneous fat.
E. Kuznitzky and E. Melchior have discussed the question of lipodystrophia
progressiva in describing the case of a very thin man, aged 20 years, with
a chalky deposit in the subcutaneous tissue at the right elbow (26), but their case
appears to me to be allied rather to those of so-called 'calcinosis' (multiple
calcification in the subcutaneous tissues), with or without the coexistence of
sclerodermatous changes (27). The atrophic process recently described by
T. C. Gilchrist and L. W. Ketron seems to be of a hitherto unrecorded kind.
Their case was that of a girl, aged 8 years, with an affection in her legs,
which the authors say is unique; it is an 'atrophy of the fatty layer of the
skin, preceded by the ingestion of the fat by large phagocytic cell-macro-
phages' (28).

I have been kindly allowed to refer to a case which may perhaps be
regarded as an 'incomplete form' of lipodystrophia progressiva, somewhat like
that of Laignel-Lavastine and Viard, to which I have alluded (9). The case

was shown by Edmund Cautley (29) at the meeting of the Harveian Society of London on February 3, 1916, and in the discussion Leonard Guthrie suggested that it might be one of lipodystrophia progressiva.   The patient was a woman, aged 24 years, whose lower extremities (excluding the feet) were remarkable for their excess of subcutaneous fat; so also was the lower part of the abdomen. The upper part of the body and face appeared thin (at all events, by contrast). The increase in the size of the legs commenced at the age of 6 years (in 1898), after an attack of diphtheria.   The patient complained of numbness in the outer parts of the legs (chiefly the left one) and breathlessness on excitement and exertion, but these troubles may have been quite independent of the abnormality in the subcutaneous fat.

In the disease known in England as 'diffuse symmetrical lipomatosis', the sides of the face, shoulders, upper arms, and back of the thorax are often specially affected, as well as the neck.   The disease should be mentioned here because to some extent the change in the subcutaneous fat is the opposite of what occurs in 'lipodystrophia progressiva'.   Moreover, it occurs almost exclusively in males.   I have seen only one case in a female (30).   The patients have practically all of them indulged in malt liquor or other alcoholic drinks. The accumulation of subcutaneous fat in the upper arms in this condition may, as I can vouch, actually hinder movements in the shoulder-joints and prevent the sufferer from getting his coat off quickly.   I have no doubt that A. Bittorf's case (31), to which Feer (13) refers for purposes of contrast, was an acute example of diffuse symmetrical lipomatosis of this kind.   The commonest clinical forms of the disease are those of the by no means very rare 'diffuse lipomata of the back of the neck', or 'Madelung's Fetthals', so called in Germany because Professor O. W. Madelung wrote about it in *Langenbeck's Archiv* in 1888 (32). In Bittorf's patient, who was a brewer, aged 28 years, a good result was obtained by thyroid treatment, and Bittorf suggested the term 'adipositas acuta symmetrica partialis, of thyroid origin'.

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SOME ACTIONS OF ANAESTHETICS ANALYSED BY THE OBSERVATION OF ALTERED CARDIAC RELATIONS TO CALCIUM

By W. BURRIDGE

(From the Physiological Laboratory, Oxford, and Guy's Hospital, London)

With Plates 17–20

SOME time ago I showed that the production of certain effects to a given intensity in hearts depressed by anaesthetics requires the presence of more calcium in the perfusing solution than is the case under more normal conditions, and, in consequence, put forward the view that anaesthesia is a state in which the body calcium has to work at a disadvantage (3). This view is concerned with the end-result of the action of the anaesthetics rather than with the developmental cause of anaesthesia, the latter quite possibly, with certain exceptions, having its explanation in some one or other of the current theories concerning the mode of action of the anaesthetics (3). For example, Verworn (17) regards anaesthesia as resulting from a disturbance of the oxidation of the tissues, but if the view be accepted that one action of calcium is to favour oxidation processes, and also the view above, such disturbance of oxidation is a necessary accompaniment of the action of the anaesthetics rather than the cause of the anaesthesis.

The additional observations on the anaesthetics given below show that they exert twofold actions on the heart of opposite type. The demonstration of a twofold action of the drugs is not new in itself, for in the case of alcohol it forms a very fruitful and perennial source of controversy. What is believed to be new is the demonstration that the twofold actions of these drugs depend on two causes, which are separated by noting their time relations both with the presence of drug and with the reaction of the heart to the calcium in the perfusing solution. Having done that it is found that each dose of drug exerts a depressing action on the heart due to one cause, and a favouring action due to another, with the result that the immediately visible action is the sum of two factors of opposite sign. Taking the amplitude of cardiac contraction as a standard for comparison the sum of the two actions tends to be greater than unity when the dose of drug is small, and less than unity with the larger doses. But within the limits of experiment given below large doses of these drugs

always give very decided evidence of augmentation, though the conditions of experiment required to demonstrate this are such as to render it improbable that any such action would be shown in the intact animal dependent on its excretory organs for any reduction in the drug-content of its blood, a necessary condition to the demonstration of the augmenting action of a large dose of drug being a sufficiently rapid reduction of the concentration of drug in the perfusing solution. Some stress has been laid on the action of these large doses of drug because it has hitherto been outside the range of controversy.

Results.

The method of experiment has been described in previous papers (2–9).

The action of alcohol may be taken first and consideration primarily given to its effects in high concentration (40 per cent.). This is a strength which, at first sight, transcends the reasonable limits of perfusion, but the experiments given elsewhere show it to be harmless if due precautions be taken in its use (3). More striking evidence is afforded by the experiments to be immediately described.

The perfused heart of a frog was used during a working day of some seven or eight hours for experiments on changes in the refractory period induced by 40 per cent. alcohol. Next day the heart was capable of beating well, and in several experiments it was confirmed that 40 per cent. alcohol produced effects similar to those obtained on the previous day. On the third day the amplitude of contraction was good, but conduction and rhythm were impaired. Treatment with the dibasic phosphate of potassium greatly improved these functions. On the fourth day rhythmic activity was still present, but the beats were only just recordable.

Now, according to Schücking (3), frogs' hearts perfused with inorganic salt solutions die after twenty-four hours, while Clark (10) considered he was highly successful in prolonging activity for two days by using lipoids, &c. The particular heart to which reference is made above was thus able to maintain activity for an exceptional length of time. The experiments afford scope for abundant discussion as to the causes favouring this prolonged activity, but the conclusion to be drawn here is the safe one, that the strength of alcohol used did not damage that heart.

This strength of alcohol stops the heart in the dilated condition and may also produce some contraction (3). If, however, the heart were examined before and after such treatment with alcohol with respect to the action of a given concentration of calcium in

(a) inducing tonus,

(b) maintaining the spontaneous contractions,

(c) shortening the refractory period,

then it was found to produce effects of greater magnitude after alcohol than before. The increased responsiveness to calcium persisted for some fifteen to

thirty minutes after the alcohol had been removed from contact with the heart, and was thus a result of some altered cardiac ' state ' (4–7).

In some of the experiments hearts that beat vigorously were caused to beat feebly by greatly reducing the calcium content of the perfusing solution. One had thus good reason for believing that the feebleness of the beats brought about by this method directly resulted from the presence of insufficient amounts of calcium in that solution. A short exposure of such a heart to 40 per cent. alcohol enabled it to beat well on the solution which just before was inadequate, though, of course, only for a time ; whereas the solution formerly enabling the heart to beat well usually evoked marked tonus during this period when the solution of diminished calcium content was capable of maintaining good spontaneous contractions.

Immediately after washing away the 40 per cent. alcohol solution from the heart it was usually possible to evoke by faradization a condition resembling tetanus when the heart was perfused with one of the usual perfusing solutions, whereas immediately before that exposure to alcohol it was not possible. This tetanic state could, however, be evoked every time in the heart perfused in absence of alcohol when the calcium content of the solution had been sufficiently increased. That is to say, immediately after alcohol one can obtain from the heart a reaction that would otherwise require an addition of calcium to the perfusing solution. To make it react ' normally ' now, calcium had to be abstracted from the solution. But the solution on which it now reacted ' normally ' was one which was unsuitable for ' normal ' activity in absence of treatment with the alcohol.

This strong solution of alcohol to some extent also resembled inhibition in its action (8, 9). No signs of activity might be shown in actual presence of the alcohol, just as in the inhibited heart, but after its removal there was the rebound to augmented activity such as the heart which has escaped from inhibition may also show.

Exposure of the heart to this strength of alcohol was only permitted for short periods, not more than thirty seconds or so. It was observed, however, that the augmenting action of the alcohol was increased as the length of exposure was increased.

The evidence so far given suffices to establish the fact that this high strength of alcohol has a twofold action on the heart. The depressing action comes and goes respectively with addition of alcohol to, or its removal from, the perfusing solution ; the augmenting action takes longer to develop and a much longer time to subside. The former predominates over the latter, so that during actual perfusion of the alcohol we cannot observe it ; but, owing to the different time relations of their subsidence, removal of the alcohol only removes the depressing action and permits of observation of the augmentation.

The two actions could be shown going on side by side if the drug were not used in such strength as sufficed to stop the heart. In such cases the primary quick depression of amplitude tended to be succeeded by a much slower increase,

the increase being in some instances sufficient to compensate the original depression. Using small concentrations of drug this compensation tended to outweigh the original depression. One obtained in fact the well-known action of alcohol in favouring cardiac activity when used in small doses. But in my experiments this favouring influence followed a primary depression, though this latter might be very small. Both the actions of alcohol showed increased intensity as its concentration became greater, but they did not increase at equal rates. With the higher concentrations the depressing action eventually predominated, the augmenting action being then observed chiefly as the 'rebound'.

Although the augmenting action of a given dose of alcohol might compensate for the original depression, wholly or in part, it did not remove that depression. Thus, suppose an experiment was begun with a heart beating at an amplitude represented on the tracing by a length h. By adding the appropriate dose of alcohol the value could be reduced by an amount a, so as now to be represented by $(h-a)$. There was a slow increase in amplitude with continuance of perfusion by a value b, say, so that the amplitude on the tracing was $(h-a+b)$. Removal of the alcohol from the perfusing solution was followed by a quick increase in amplitude equal to a, the original depression. The value of the amplitude was now $(h+b)$, i.e. it was greater than that at the commencement of the experiment by an amount equal to that which was added subsequent to the primary depression produced by the alcohol. From this value it gradually returned to the original.

It did not matter at what stage the alcohol was removed. With the reservations mentioned below, removal of the alcohol at any stage was followed by a sudden increase of contraction equal to the original depression. Whatever increase had taken place between the original depression and the subsequent augmentation persisted and was added to the original amplitude.

The performance of these quantitative experiments requires that the value $(h+b)$ shall represent a quantity equal to or less than the maximum possible amplitude of contraction. If it were otherwise a qualitative result only would be obtained. It would be possible to demonstrate that after perfusion of alcohol there may be an increase in the amplitude of contraction, but not that the increase was equal to that taking place during perfusion of the alcohol. In turn, that means that the experimenter must have knowledge of the capacity of the machine with which he is working and be in a position to make the selection of perfusing solution on which the heart beats with a sufficient reserve of contraction to permit of the demonstration of these relations. Perfused with most inorganic saline solutions the heart has not the necessary reserve ; these solutions being rather devices for running the machine ' all out '. (See Fig. 1.)

Vernon (16) also observed an increased amplitude of contraction persisting after removal of alcohol from the perfusing solution. To his results there is added the fact that the amount of this augmentation is increased by increased length of exposure of the heart to the alcohol as well as on its concentration.

During this augmenting action of alcohol the heart was more responsive to

calcium than before. The development of this state of increased responsiveness was antagonized by calcium. Thus, if the calcium content of the perfusing solution were too high, such as that of solutions formerly used by me, for example (3), the augmenting action of the smaller concentrations of alcohol was not observed. Instead, after the original depression, the beats were maintained at a constant depressed level. The big dose of alcohol overcame the antagonizing action of calcium and the augmentation was observed as a 'rebound'. Using solutions of varying composition that rebound is traced back to actions taking place during the perfusion of alcohol in strength compatible with visible cardiac activity. Some of these actions of alcohol are illustrated in the accompanying diagrams. (See Fig. 2.)

A comparison of the experiments above with those on adrenin in this number of the Journal shows some similarities in the actions of these two substances. Both exert similar actions on the heart bearing similar relations to calcium, though showing vast quantitative differences. Assisted by potassium, for example, as demonstrated elsewhere, alcohol has induced the frog's heart at room temperature to beat some eighty times per minute (3). To explain these phenomena of augmentation induced by alcohol it does not seem to me to be necessary to invoke an actual stimulation of sympathetic nerves. The action of alcohol can transcend the latter. The better explanation appears to be that both agencies have certain actions in common. A similar action by different agencies fits also the resemblances of certain other actions of alcohol, as well as of adrenin, to inhibition and 'inhibitory rebound' (8, 9).

The experiments above are of interest in connexion with the pathology of alcohol. Although each dose of drug exerts two actions it is possible to make either action predominate by selecting the appropriate dose. The particular selection is usually empirical. Some seek oblivion by quaffing deeply, others seek a tonic by taking a little often. To this latter group some further attention may be given.

We know that the members of this group eventually reach a condition in which continued intake of drug becomes essential to their subjective feeling of normality, and that this subjective feeling is to some extent confirmed by certain objective untoward symptoms liable to arise on the sudden withdrawal of their wonted stimulus. The individual in the later stages has got 'accommodated' to the drug. The possible origin of such accommodation may be as follows :

By taking a little often the individual takes into his system the drug in doses which allow of predominance of its adrenin-like action. 'Accommodation' to this could be brought about by an alteration in the 'state' of the tissue, or by an alteration (diminution) in the calcium tension of the perfusing solution. In the former case the 'state' of the tissues in absence of the drug would be subnormal, the deviation from the normal being equal to that customarily added by the drug. The tissues are below 'par', and by the alcohol are brought up to 'par'. In the latter case the addition of the drug enables tissues in a more

or less normal 'state' to work on what has now become an inadequate perfusing solution in absence of the drug. Possibly both factors are at work, but I think the change in perfusing solution predominates. The grounds for the belief are the similarities which the chronic alcoholic on sudden withdrawal of alcohol presents to the subject of hyperthyroidism. It is not suggested that the two diseases themselves are similar. The subject of hyperthyroidism always shows the defects due to altered blood state (1), whereas the chronic alcoholic will show his rather acutely when his tonic is suddenly withdrawn. The altered blood is a factor common to two complexes. The symptoms produced by it will not only be modified by the other factors of each complex, but they will also only form a limited portion of that complex. The term 'tremor', for instance, has a similar denotation for each, but a different connotation. The individuals have, however, a certain liability which leads the anaesthetist to avoid them if possible, and another that leads to the final prescription containing stro-phanthin or something similar. Their common weak point is their circulation. In both cases the weak point is such as would arise if the heart had not a perfusing solution of adequate calcium content.

One can also see that the chronic alcoholic should apparently have some difficulty in giving what may be called a plus augmenting reaction to alcohol. A dose of alcohol that would augment the circulation of a more normal individual probably has the same action in the alcoholic. The latter, however, is handicapped because of the altered relations between his heart and its perfusing solution. Part of the augmenting action of the drug has to be utilized in bringing the circulation back to normal, and it is only if there be any augmenting action left over after this that one can get evidence of a supernormal reaction. The possibility, even probability, however, can be conceived that the amount of drug required to bring the alcoholic's circulation up to normal is the maximum amount consistent with augmentation. Wherefore, although the statement that the amount of alcohol required to produce a super-normal reaction in the heart of a chronic alcoholic is an amount that would only give visible depression, seems paradoxical, it will yet be found to express a certain possible truth.

Ether. The action of ether on the heart presents the same general features and relations to calcium as does the action of alcohol. But its augmenting action was much greater in proportion to its depressing action than was the case with the latter.

In my experiments the depressing action appeared first and was succeeded by the augmenting action, though where the dose was small (0·2 per cent.), the depressing action was very small in comparison with the augmentation suc-ceeding it. The greater the calcium content of the perfusing solution, the greater the dose of ether required to demonstrate this augmentation. Like alcohol, too, the bigger doses of ether, sufficient to give only phenomena of depression during actual contact with the heart, were followed by phenomena of augmentation immediately after removal of the drug.

Schultz (14), using strips of cardiac muscle, also found phenomena of augmentation, as evinced by summation of contractions, &c., immediately after exposure to saturated ether. He states, however, the compound contractions obtained by summation under these circumstances were less in amplitude than the single spontaneous contractions of the unpoisoned heart. His results as regards amplitude were possibly due in part to non-recovery of the whole of the strips after the original poisoning. In the perfused heart I found the compound contractions to reach an amplitude about the same as the maximum of the unpoisoned muscle after exposure to a saturated solution of ether, while the refractory period was so shortened that a condition resembling tetanus was possible. This shortening was, however, temporary, was at its maximum immediately after the ether had been washed out of the heart, and then gradually returned to the normal. But if one portion of the muscle had still ether in it, while at the same time another portion had the ether washed out of it, as is quite possible when strips of muscle are merely washed in baths, then, although the recovered portion gives a summated contraction as great as the normal spontaneous contraction of that portion, the non-recovered portion does not become excited. There will be later a period when all parts have recovered, but by the time that has happened the change has possibly begun to subside in the portion that recovered first, so that the compound contractions may still fail to reach those single contractions of the unpoisoned heart. Such possible sources of error are diminished to a minimum by a suitable perfusing method. An example of the full action is given in Fig. 3.

Vernon (16) also found that augmentation might follow the original depression which was due to the use of a sufficient dose of ether, and suggested that some stimulation of augmentor nerves might explain the results observed. My own experiments, however, present this action as due to a cause which can lead also under the appropriate conditions to stoppage of the heart in systole, to simulate the 'inhibitory rebound', or to lead to the production of a condition resembling tetanus in the heart. It is better, I think, to suggest that ether and sympathetic nerves give rise to different grades of a cardiac condition w ich can be designated as an increased response of the heart to calcium.

Chloroform. Chloroform has also a twofold action on the heart similar to that described for ether and alcohol. Its augmenting action was relatively much less than that of the other two substances, though it was possible to get the appropriate combination of heart, chloroform, and perfusing solution so that the heart in presence of chloroform beat with greater amplitude than before. The increase of amplitude persisted for some little time subsequent to removal of the chloroform from the perfusing solution, and then the beats returned to their original value. Neither Sherrington and Sowton (15) nor Vernon (16) appear to have recorded any such action of chloroform on the perfused heart, possibly on account of the calcium content of the perfusing

solutions they used. I did not obtain it when I used solutions of relatively high calcium content. The action is shown in Fig. 1 B.

The favouring action of chloroform outweighed its depressing action in the particular experiment just recorded, but on pushing the drug this relation was reversed. But even if the drug were present in amounts sufficient to stop the heart in the dilated condition, its removal, especially if it were allowed to remain in contact with the heart a few seconds, was followed by a ' rebound ' to a condition of greater activity than was the case before the drug was used. As with alcohol and ether, the depressing action of chloroform came on immediately after its addition to the perfusing solution, and disappeared immediately after its removal therefrom, whereas the augmenting action showed a time factor in its appearance and especially in its disappearance.

The signs of augmentation observed after chloroform were connected with those appearing during its perfusion by the obtaining of quantitative results similar to those already dealt with, though in some cases when working with the higher concentrations the connecting links were missed. Instead there was a ' simple ' rebound. The latter will not be dealt with here as it is best studied in connexion with certain other drugs.

Both series of effects were observed by Sherrington and Sowton (16), who suggested, in explanation of those appearing during perfusion of the drug, a gradual accommodation of heart to drug, and for those appearing after the drug was removed, an excitation of sympathetic nerves. Vernon (17), however, suggested that an excitation of sympathetic nerves explained what Sherrington and Sowton (16) would apparently have regarded as an ' accommodation ' to ether. For both series of phenomena I prefer the suggestion given earlier, namely, that these drugs and sympathetic nerves have certain actions in common. The quantitative experiments performed with these drugs serve to connect certain actions observed during their perfusion with other actions observed after their removal. But when these drugs are used in high concentration their stimulating action exceeds that normally associated with stimulation of sympathetic nerves.

There is a certain degree of importance to be ascribed to the twofold action of the drug used in high concentration. Repeated exposure of the perfused heart to Ringer's solution saturated with chloroform has not hitherto been regarded as a measure capable of exercising a tonic action on the heart. When I first observed the phenomenon myself I was led to suggest that some form of damage to the cardiac mechanism analogous to loss of central inhibition might account for the phenomena of augmentation observed after the employment of measures apparently capable only of causing damage to the heart (3). But experiments made since have shown that the local inhibitory mechanism of the heart is submerged (9), as it were, directly after the perfusion of an inorganic saline medium, and a more varied choice of perfusing solution shows the stimulating action of a high concentration of drug to be an advanced degree of that observed with the low concentrations.

Evidence of a tonic stimulation produced by a high concentration of chloroform should be difficult, if not impossible, to obtain in experiments done on the intact animal, since the possibility of its observation depends on the rate of withdrawal of the drug. There is also a lower limit to the concentration of drug since an experiment is ended when enough is present to stop the heart. From the effects observed in the perfused heart we can see that removal of the drug is immediately followed by loss of its depressing action, whereas its augmenting action much more slowly subsides. The intact animal, however, effects a gradual diminution in the concentration of drug in the blood by excreting it via the lungs, &c., whereas in the perfused heart there is a simple and sudden change. The amount of augmentation that can be observed as an 'after-effect' depends on the amount of depression removed in a given unit of time, because we get evidence of it by its persistence after removal of the depression. But the augmentation persists only for a limited time, so that if the depression be removed at anything like the same rate, or slower than the rate of subsidence of the augmentation, we can get no definite evidence of that augmenting action. It is simply merged or submerged in the gradual improvement consequent on the gradual withdrawal of drug.

Chloroform has also an action on the contractile material of the heart distinct from its actions on cardiac excitability, the actions mainly considered above. The independence of the actions on excitability and contractility has been pointed out before (3), but the experiment to be immediately described shows it, perhaps, somewhat better.

The maximum contractility of a heart was first ascertained by the potassium method (6), and then a perfusing solution selected which contained sufficient calcium to permit the heart to beat at approximately this maximum amplitude. A second perfusing solution was next selected containing much less calcium than the foregoing—usually about one-fifth—and such that the heart only beat feebly on it. Having thus obtained two suitable solutions, the heart was exposed to a solution of chloroform for a length of time sufficient to cause it damage. Following on this exposure, the amplitudes of the beats on the two solutions were again ascertained.

There were, thus, two sets of observations as to the amplitudes of the beats on these two solutions; one set taken before exposure of the heart to chloroform, the other set taken after that exposure. The results showed that, provided damage had been done to contraction, the heart beat at a lower amplitude on the solution of high calcium content after exposure to the chloroform than was the case before such exposure, and, provided the damage done were not too great, the beats of the heart were greater in amplitude on the solution of low calcium content after the chloroform than they had been before.

The explanation of the results is simple. The experiment was begun with a certain capital stock of contractile material approximately represented by the amplitude of the beats when the heart was perfused by the solution of higher calcium content. The chloroform destroyed some of that capital, so that

perforce, subsequently, the beats were diminished on perfusion with that solution.

But only a certain percentage of this stock of contractile material was thrown into action when the heart beat on the solution of lower calcium content, and it so happened that the amount represented by the larger percentage on a diminished capital was greater than that represented by the smaller percentage on the original capital. In both sets of experiments, of course, the beats of the heart on the solution of lower calcium content were smaller than those on the higher.

Chloroform has also a twofold action on the summation line in the faradized heart, the height of this line being first quickly depressed and then more slowly raised by the drug. The raising of the line, like the other augmenting actions of the drug, tended to persist after the chloroform was removed from the heart. After large doses of chloroform summation of contractions and a condition resembling tetanus was produced, though not always so. Some of these effects are illustrated in Fig. 4.

The heart was faradized continuously between the signs shown in the diagram, faradization being begun before the chloroform solution was perfused. The summation line in its earliest stages thus represents the reaction of the heart to the perfusing solution itself. Chloroform in known amounts was next added to the perfusing solution and the pressure of perfusion immediately raised because of the otherwise great length of time required for the solution to pass through the partially contracted heart. The time taken for the new solution to replace that already present in the heart and cannula was sufficient to allow the effect of the increased pressure on the summation line to be established before the chloroform made its presence felt. The summation line is affected by an increase of pressure in various ways. It is raised, lowered, or unchanged— alterations of perfusion pressure may produce similar effects—on the base line of the spontaneous contractions. The effects are mechanical and depend in some measure on the condition of the auricles. Auricles in good tone dilate, but if already dilated, the pressure bulges them laterally, and so causes approximation in the vertical direction. The effect of the former (dilation) is to lower the summation line, of the latter to raise it. The lateral bulging and vertical shortening of the auricle seems somewhat on a par with contraction of the sarcomeres as described by Macdougall. The state is readily induced if the ventricle be in a condition of persistent contraction. The double action of chloroform on the summation-line period is shown in the first illustration of Fig. 5. Perfusion of the chloroform solution at high pressure was begun as marked. The action of the chloroform is not shown for some seconds later, the slightly primary variation in the tracing being the effect of pressure.

The second illustration shows the action of a distinctly larger concentration of chloroform. In this second case a series of alternating perfusions of the perfusing solution itself and of perfusing solution plus chloroform was made

through the continuously faradized heart. The depressing action was well marked during perfusion of the drug, but there was little sign of any subsequent improvement while the chloroform was present. But on removing the chloroform it was evident that something in addition to the depression had happened, because the summation line on the perfusing solution itself was now at a higher level than it had been before the chloroform was used. In this case the favouring action of chloroform was shown as a simple 'rebound'. This was frequently the case when the higher strengths of chloroform were used. The improvement associated with the rebound persisted for some little time and did not appear to be affected by a further perfusion of chloroform, for on doing this the summation line was again depressed, and, as on the first occasion, when the chloroform was removed, the summation line on this second occasion was higher than it was after the first removal of the drug. There appeared, indeed, to be a summation of improvements. Each perfusion of chloroform was followed by a further raising of the summation line as compared with what it had been before that particular perfusion of drug was made.

Some Relations between the Anaesthetics and Adrenin.

From the actions of the anaesthetics dealt with above, and the actions of digitalis and barium (7) considered in a previous paper, it will have been gathered that a source of error is brought in when the action of a drug on the heart is considered apart from its concentration and the composition of the perfusing solution. We can get further evidence on this by taking certain relations between the anaesthetics and adrenin.

The anaesthetics and adrenin (9) have each a twofold action on the heart, of similar type but showing vast quantitative differences in the relative intensities of the two stages. The augmenting action of adrenin tends to be predominant, and it is normally used in such concentration as allows that action to be predominant, whereas, with the anaesthetics, their depressing action tends to predominate, and they are usually employed in such concentration as allows it to be predominant. If, however, we transgress these customary limits, we open up the possibility of mutual reinforcement and antagonism, or of compensation.

We may consider compensation first, since this has already been dealt with by Gunn (11) as an antagonism.

An illustration showing this compensation is given in Fig. 5.

The heart of which the beats are there recorded was perfused with a strength of chloroform just sufficient to stop it in the dilated condition. Adrenin was added to the perfusing solution and beating restarted. Gunn (11) states that adrenin cannot restart beats in a heart stopped by chloroform, but his statement possibly rests on the use of a too great concentration of adrenin. To restart the beats under these conditions the dose of adrenin must be

sufficiently small, otherwise it may become an additional depressant to the heart.

When the beats thus restarted had been in progress a short time the adrenin-anaesthetic mixture was washed out and a Ringer alone substituted. The beats of the heart now became greater than they had been before the experiment was begun. The point to which attention is drawn is that they are greater by a quite definite amount, namely, that of the contractions initiated by the adrenin. The heart beat with this increased amplitude for some little time longer, and then returned towards the condition prevailing at the commencement of the experiment.

The conclusion to be drawn from these experiments is the at first sight paradoxical one, that the adrenin had not really got rid of the depressing action of the chloroform. This depressing action was quantitatively represented by the height of the original contractions. That amount of depression was still present when the adrenin-chloroform mixture was removed from the heart, as was shown by the fact that the increase in amplitude now taking place was equal to that of the original contractions. The adrenin had thus not removed this depression, but had brought into being a state of the heart enabling it to beat in presence of this depression. And that state of the heart persisted when the adrenin-chloroform mixture was removed from the heart, whereas the depression disappeared. Such effects were not observed when the action of anaesthetics was antagonized by calcium.

The antagonism in the latter case may be, perhaps, compared with that of balancing weights in an ordinary scales, whereas in the former a balance is obtained by shifting the fulcrum about which the weights revolve. The simultaneous removal of the weights is followed by a return to the *status quo ante* in the one case, but not in the other.

The events depicted in Fig. 6 are also of some interest. In the experiments there recorded alcohol was added to Ringer's solution in amounts just about sufficient to stop the heart in the dilated condition. Adrenin was next added to this mixture, and not only enabled the heart to beat again, but also to beat at a greater amplitude than was the case when the experiment was begun. This adrenin-alcohol-Ringer mixture was then replaced by Ringer's solution alone, and following on this substitution there are to be observed two series of events. The one series occupies a period of some fifteen seconds, during which three main phenomena are to be noted, viz. :

1. An increased amplitude of beat ;
2. An increased rate of beat ; and
3. An increase of tonus.

The increase of rate and tonus ceased rather abruptly and were succeeded by the second series of events, or period of gradual decline. The latter was not complete at the point where the tracing ends.

Now, the maximum contractions shown on this tracing were also the maximum possible for that heart, so that if the depression originally produced

by the alcohol had not been removed, but only compensated for by the adrenin, and so was still present when the alcohol-adrenin mixture was replaced by Ringer alone, only about one-half of that depression was capable of expression as an increase of amplitude following on the replacement because that addition to the amplitude then in vogue carried it to that maximum. The increased tonus and rate presumably represents the other half of the energy set free when the alcohol was removed. It would also appear that these functions can be mediated by some one underlying cause.

When examining the relations between adrenin and choral hydrate, Gunn (11) found that the former did not antagonize that action of the latter whereby the heart was sent into systole. My own experiments rather indicate them to reinforce one another in this action. The systolic state induced by chloral hydrate is the result of a changed responsiveness of the heart to calcium induced by that drug. A mixture of chloral hydrate and adrenin may give greater tonus than the former alone. An example is shown in Fig. 7.

In the experiment it will be seen that the heart was sent into tonus first by using a 1 per cent. solution of chloral hydrate in Ringer's solution. The rise into tonus was sharp at the outset, and then the rate of addition of contracture began to decrease. When, as judged by a previous experiment on that same heart, the amount of tonus induced by the chloral hydrate alone had reached its maximum, adrenin was added to the solution. There then ensued some relaxation, also observed by Gunn, which was followed by a further increase of tonus. The relaxation we may assign to the primary depressing action of adrenin (9). It should be noted about the subsequent increase of tonus, that it took place in two stages, the first part being carried out quicker than the latter. The introduction of the adrenin, thus, increased the rate at which tonus was produced as well as its amount. It will probably also be noted that the increased rate of tonus increment was about equal to that taking place in the first stage of the action of chloral hydrate alone, but was much slower than the rate of shortening associated with the spontaneous contractions.

Concluding Remarks.

The experiments above are adequate to establish a twofold action of the anaesthetics on the heart. Each action has been expressed as an alteration in the response of the heart to calcium, but as being of opposite signs and bearing different time relations to the presence of drug in the perfusing solution. There can also be little doubt that anaesthesia depends on the 'surface' action of these drugs.

Now, Höber (12) has shown that the anaesthetics produce changes in the state of aggregation of the colloids of the tissues on which they act, and regards these changes in aggregation as responsible for the anaesthetic state. The changes produced by them are those of a finer state of subdivision, and

incidentally of opposite type to that induced by calcium. Höber found the latter
to stabilize the colloids.

One marked feature of altered states of aggregation is that the return to the
original state lags behind removal of the agency originally producing the altera-
tion, and tested by this, we are led to conclude that the phenomena of exaltation
observed with the anaesthetics are those due to the alterations in state of
aggregation. The cause of anaesthesia would thus appear to be some agency
different from that suggested by Höber. Indeed, it is not impossible that what
Höber regards as the cause of anaesthesia is a secondary consequence of a more
fundamental action just as with Verworn's hypothesis (17). The anaesthetics
hinder the action of calcium. In the original equilibrium of the tissues that
calcium was a factor in determining the state of aggregation of the colloids,
tending to coagulate them. The result is that the state of aggregation falls
away from that originally maintained by this element. The subsequent course
of events is then made clear if one bears in mind the twofold action of calcium
itself and certain apparent paradoxes associated therewith. The state of
aggregation maintained by calcium, its 'deep' action, is one inimical to those
of its actions I have elsewhere termed 'surface' actions, so that if we hinder
this 'deep' action we shall facilitate its 'surface' ones (4–9). The anaesthetics
by one action hindered the 'surface' actions of calcium and by another the
'deep' action of that element, but in hindering its 'deep' action they facilitated
the 'surface' actions.

The mode of action of the anaesthetics will not be discussed beyond pointing
out that certain actions of calcium are facilitated by phosphates (7), and that
the anaesthetics can disturb the phosphate metabolism of the heart (3). It is
possible to surmise that the solubility of the anaesthetics in certain phosphorized
fats (Overton, Meyer) may be a factor determining the end-result noted above.

Another point to which attention may be drawn is that relating to the
antagonizing action of calcium on the action of the anaesthetics. Experience
has shown that a vapour containing 2 per cent. of chloroform is a safe
anaesthetic for a normal individual. Expressed in terms of the work above,
we may say that the effective tension of calcium in the blood is such that it is
adequate to carry on the circulation in presence of 2 per cent. of chloroform
in the air breathed.

If, however, the individual have a calcium tension of the blood lower than
normal, that percentage of chloroform which would be just adequate to permit
of carrying on the circulation in the normal would be too great. This would
account, in part at any rate, for the additional risk which anaesthesia entails in
subjects of chronic alcoholism or hyperthyroidism.

The twofold action of the anaesthetics also enables them to develop
phenomena resembling inhibition when employed in the appropriate dose. If
the dose be large enough the heart quickly stops in diastole, but rebounds to
augmented activity when the drug is removed, just as may the heart which has
'escaped' from inhibition. The essential mechanism of inhibition, as I have

given it elsewhere, is essentially of the same kind as that I have suggested to underlie the anaesthetic action of chloroform. Here again one runs against the individual with low calcium tension. The ease with which the heart is inhibited increases with decrease in the calcium tension of the perfusing solution. The individual with a too low calcium tension of the blood has thus a double danger. His heart is more readily inhibited from within than is normal, and also more readily brought under the influence of agencies coming from without.

Summary of Conclusions.

1. The anaesthetics, alcohol, chloroform, and ether, have each a twofold action on the heart:

> (a) a depressing action reached quickly on addition of drug to perfusing solution, and disappearing directly after its removal;
>
> (b) a favouring action which shows a time factor in its appearance and especially its disappearance.

2. When the depressing action is present more calcium must be added to the perfusing solution to produce effects of a given intensity, e. g. to evoke contractions of half the maximum possible amplitude, than is the case in absence of drug.

3. The favouring action is associated with an opposite relation to calcium.

4. The two actions varied with each drug and with its concentration.

5. Certain relations between adrenin and the anaesthetics are considered.

6. Some suggestions are made concerning the pathology of alcohol.

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DESCRIPTION OF FIGURES.

PLATE 17. FIG. 1 A. At ↪ 1 % Alc., 1 per cent. alcohol perfused in Ringer's solution. The beats are first quickly depressed and then more slowly increase in amplitude. In this case they reached the maximum.

At ↪ CaHP Ringer's solution alone perfused. The beats gradually return to normal.

FIG. 1 B. Primary depression followed by augmentation taking place under the influence of chloroform. In this case when the augmentation was at its maximum the chloroform was removed from the perfusing solution (CaHP), with the result that a further augmentation equal to the original depression took place, followed by a slower subsidence and return to normal.

FIG. 1 C. Similar to 1 B, but with ether.

FIG. 1 D for comparison.
Here the beats are depressed by magnesium chloride and the augmentation takes place under the influence of adrenin (*Adr.*). On removing both magnesium and adrenin there are—
(1) Removal of 'magnesium' depression—sudden sharp increase equal to the original depression.
(2) Removal of adrenin augmentation—slow subsidence of amplitude.

FIG. 2 A. Shows the gradual rise in the height of the summation line obtained on faradization, which presumably corresponds to a shortening of the refractory period, taking place under the influence of alcohol (3 per cent. in Ringer). Between the marks + and ↑ the heart was faradized. Note staircase phenomenon after each period of faradization.

FIG. 2 B. Shows the possibility of obtaining a condition resembling tetanus immediately after use of a large dose of alcohol.
↪ NS.   Ringer alone perfused.
↪ 40 per cent. Alc.   40 per cent. alcohol in Ringer perfused.
S . . .   These contractions are evoked by single induced shocks.

PLATE 18. FIG. 2 C. As 2 B, but showing a quicker return to the *status quo ante*.

FIG. 3. Shows a great summation and fusion contractions on faradization taking place after ether. Note gradual subsidence.

PLATE 19. FIGS. 4 A and 4 B. The hearts were faradized continuously between the marks + and ↑ (3–4 minutes in A and B).

Perfusion was carried out at high pressure owing to the difficulty of getting fluid to pass through the partially contracted heart. In these cases whenever there was a change in perfusion pressure—as occurred each time solutions were changed—there is an alteration in level of the summation line.

The rise between marks ﹡. . . . . .﹡ are due to such changes. Between *Po* and some other signs the perfusion pressure was zero, *Po* representing the point where perfusion of one solution ceased and the next sign (e. g. *NS.*) representing point where perfusion of the next solution was begun. It will be observed that at each point marked *Po* the summation line falls, and there is a primary rise at commencement of each new perfusion.

FIG. 4 C. Shows primary fall and secondary rise of summation line produced by Ringer's solution, one-twentieth saturated with chloroform.

PLATE 20. FIG. 5 A. ↑ $\frac{1}{20}$ CHCl$_3$ = Ringer's solution, one-twentieth saturated with chloroform at 15° C.
1×10.7 Adr. = addition of adrenalin hydrochloride to chloroform solution to make 1 pt. in 1,000,000 of same.
2 R = Ringer's solution only perfused.
$\frac{1}{20}$ CHCl$_3$ + Adr. = Solution containing both chloroform and adrenalin, as above, perfused.

FIG. 5 B. Heart stopped by chloroform and restarted by Ringer alone. Then stopped again by chloroform, but this time restarted by adrenalin. On washing away the chloroform-adrenalin solution the beats are now greater than at commencement by the amount added by the adrenalin. See also Fig. 1 D.
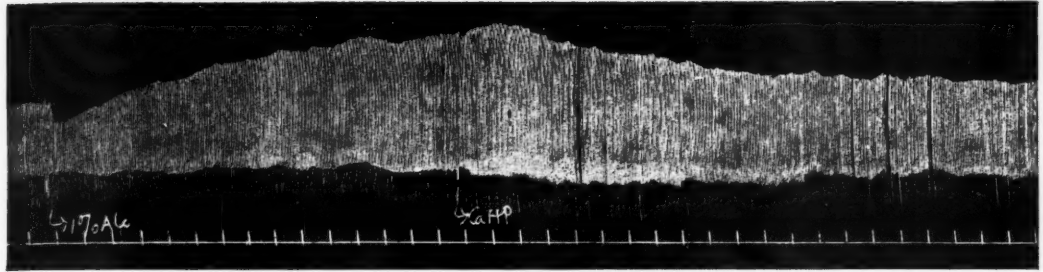
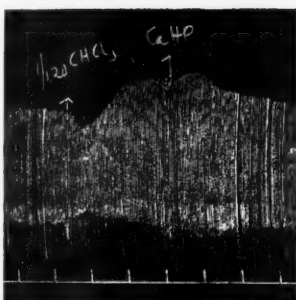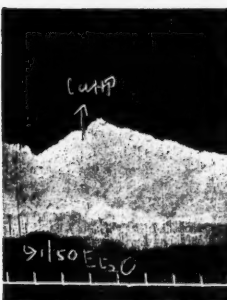FIG. 6. Description in text:

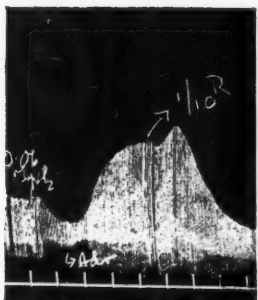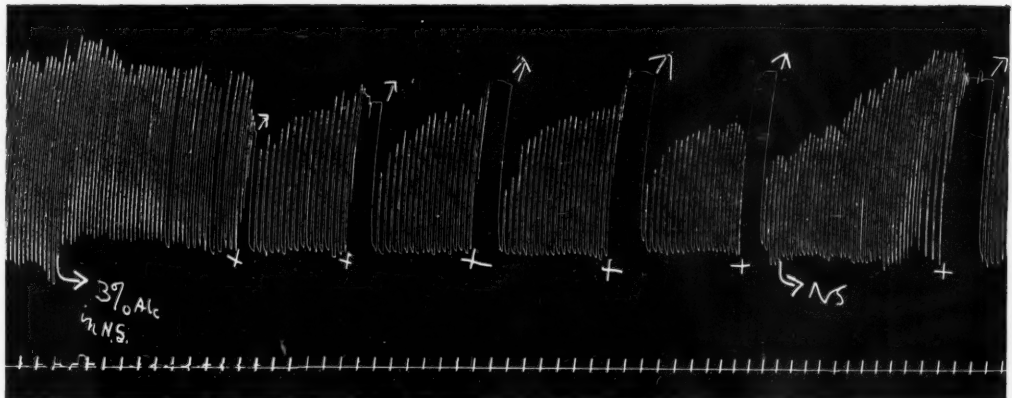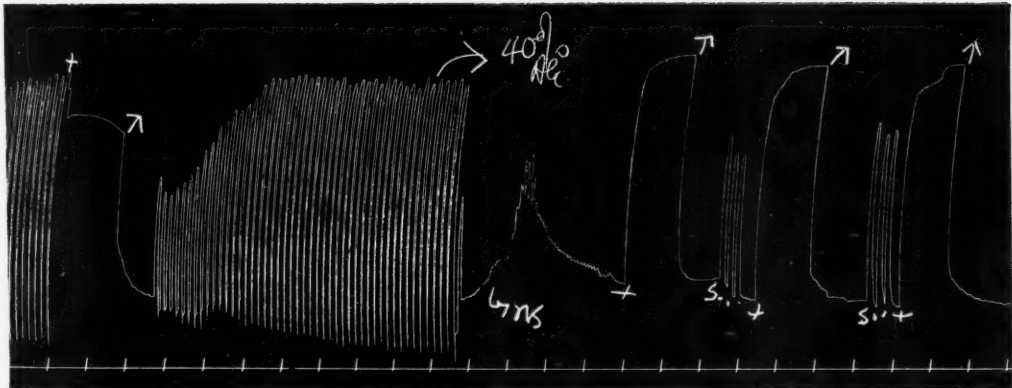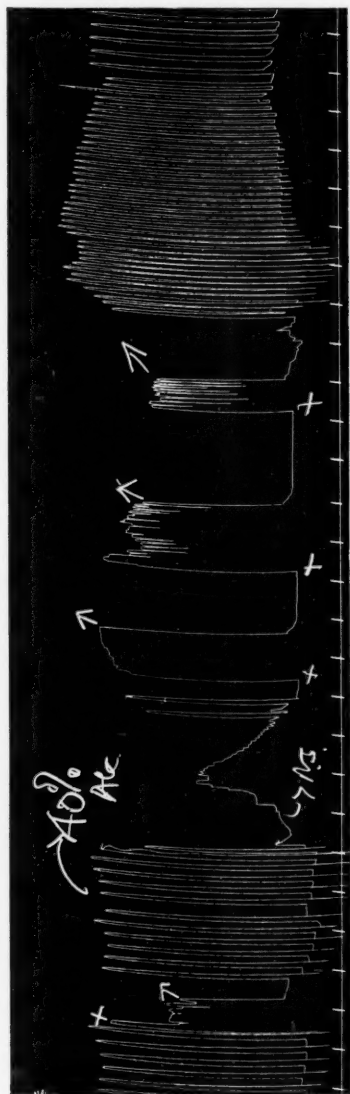FIG. 7. Description in text.

FIG. 1 A
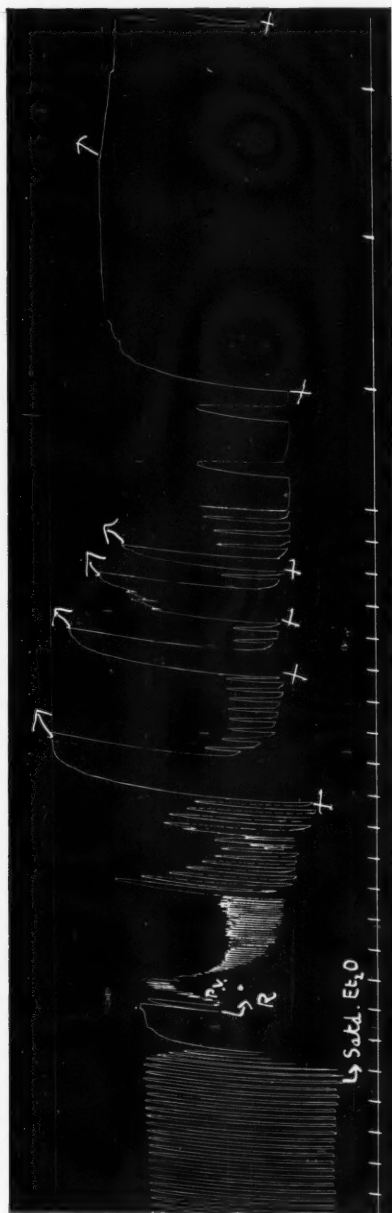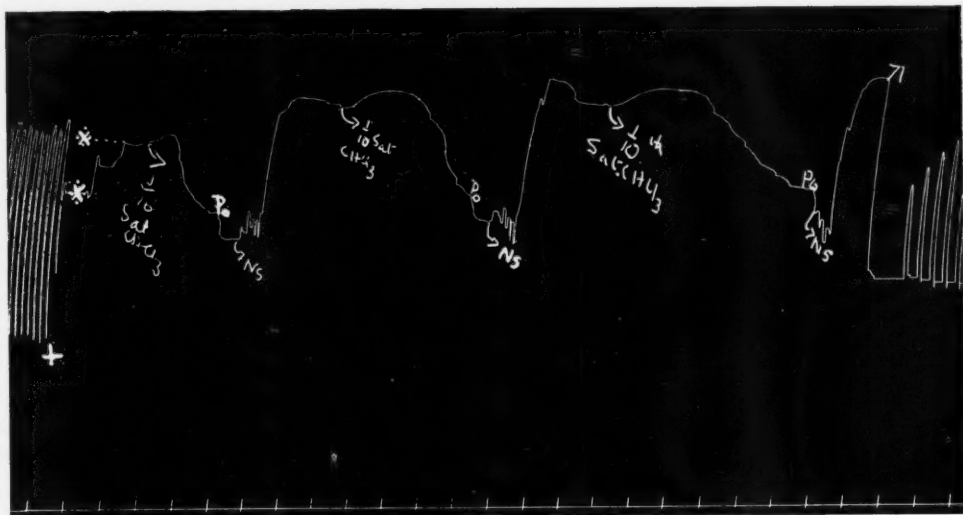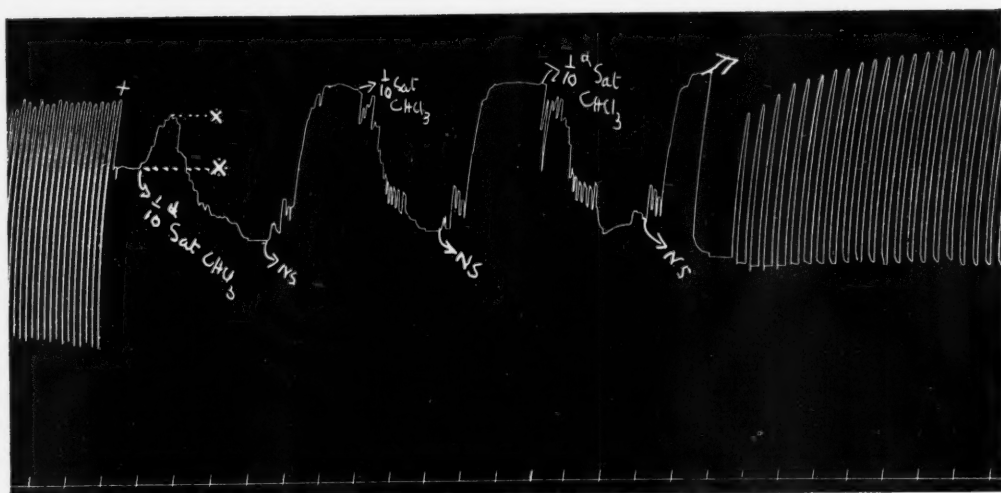

FIG. 1 B

FIG. 1 C

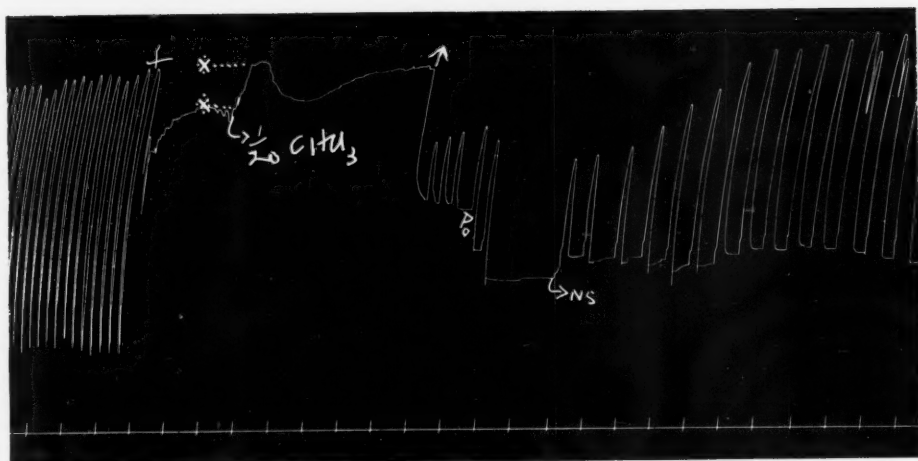FIG. 1 D

FIG. 2 A

FIG. 2 B

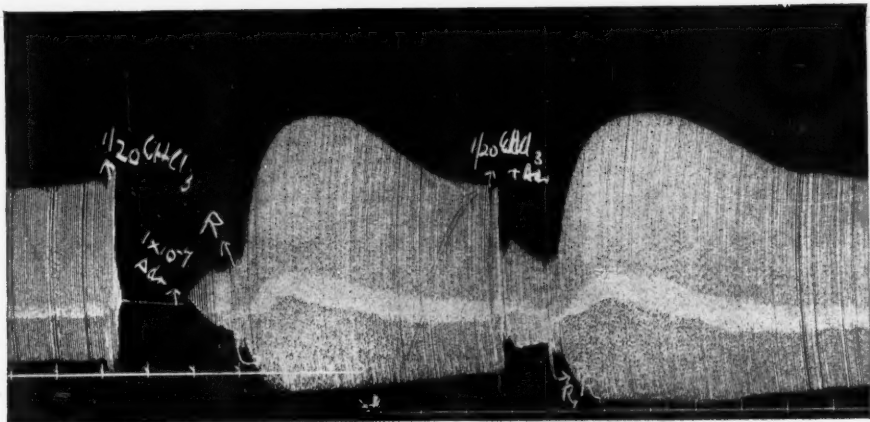FIG. 2c

FIG. 3

FIG. 4 A
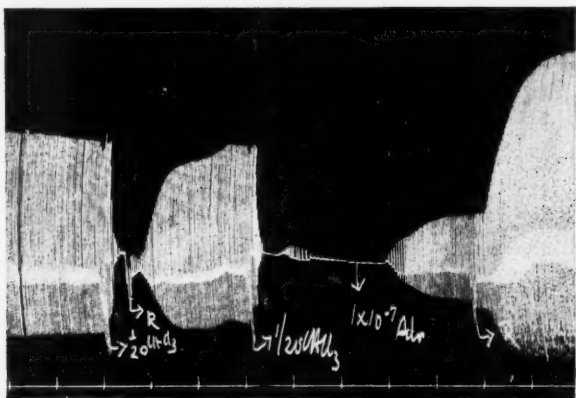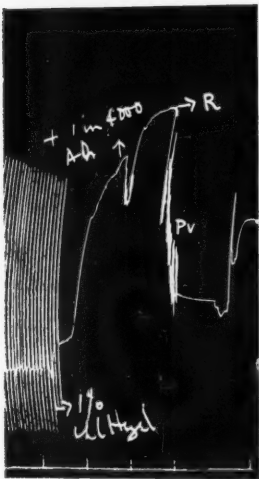

FIG. 4 B

FIG. 4 C

FIG. 5 A

FIG. 5 B

FIG. 7
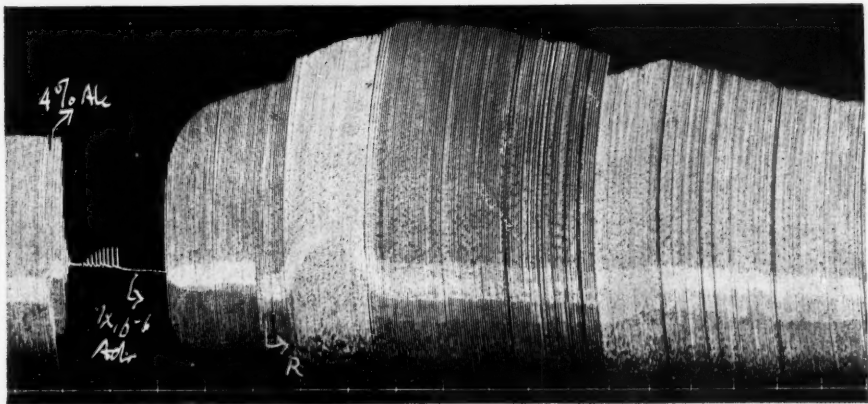
FIG. 6

RESEARCHES ON THE PERFUSED HEART

AN ACTION OF STRYCHNINE, ETC., WITH SOME REMARKS ON TETANUS

By W. BURRIDGE

(From the Physiological Laboratory, Oxford, and Guy's Hospital, London)

See Plate 21

HERE and there instances are found in which the clinical indication for the use of a drug is not confirmed by the experimental evidence. This may either be the result of the clinician being in error, or limitations to the ordinary experimental methods. One possible source of error in the latter is the great care normally taken to experiment on perfectly fresh and healthy material; for, where there is a sudden change from the normal to the pathological, it is possible that the action of a drug on the normal heart may not furnish the key to its use in such pathological condition, though it does in conditions arising more gradually.

During the course of certain experiments, not herein described, there was occasion to make healthy hearts abnormal. When so made abnormal they were exposed to the action of various drugs and agencies. The experiments showed that in a particular abnormal state three drugs—strychnine, atropin, and ergotoxin—produced effects not observed under more normal conditions.

In the normal perfused heart each of these drugs in large doses depresses the amplitude of contraction, the usual view of the action regarding it as a weakening of the muscle fibres. I did not find, however, that the depressing action of these drugs on spontaneous contractility was accompanied by any corresponding diminution in the amplitude of the contraction evoked by potassium chloride, i. e. the contractile substance can still contract fully.

I did find that when their depressing action was present, the heart became less responsive to calcium than was the case before, and that their depressing action could be overcome temporarily by adding more calcium to the perfusing solution. It was also antagonized by adrenin and digitalis.

But in these abnormal hearts there was found the entirely different action shown in Plate 21. A decided augmentation of cardiac activity was now produced, which, however, was temporary under the conditions of the experiment.

The 'state' of the heart produced by these drugs was the same in the

abnormal as the normal heart, and is responsible for the failure succeeding the preliminary augmentation. The explanation of the augmentation depends on the nature of the abnormality present.

The hearts in which this action took place had been rendered abnormal by a process of relative decalcification which had taken place chiefly under the influence of sodium. Some of the experimental evidence on this point is given elsewhere (1). The process required some time, but when the preparatory period was over, then the action of these drugs shown above was obtained.

The hearts could be rendered capable of working more normally by altering their 'state' so as to make them more responsive to calcium than was actually the case, but, as we have already seen, these drugs influenced the heart in the contrary direction. The improvement which immediately followed their use was not, then, due to any such cause.

In addition to the abnormality shown in the tracings above, various methods of analysis showed the presence of other abnormalities in those hearts. We need not discuss them here save to remark that they disappeared on increasing the amount of calcium in the perfusing solution, or on replacing some of the sodium by some such inert body as cane sugar. These facts, together with the conditions governing the production of this abnormal state, lead me to conclude that this action of these drugs results from a power to enable tissues to take up more calcium from the perfusing solution than would otherwise be the case.

This explanation together with a modification of Macdonald's theory of inhibition (9) explains also many other actions of these drugs. Macdonald considers that the inhibited tissue is one in which the colloids are in a very high state of subdivision consequent on the receipt of a positive charge. In consequence there is a withdrawal of potassium salts from solution, to be packed away on the surfaces of the colloids. But I have shown elsewhere that the positive charge carried by the hydrogen ion has a decalcifying action on the heart (2), so that to Macdonald's theory we have to add that, in addition to the finer state of subdivision, there is an inability on the part of calcium to combine with these colloids. This decalcification due to the receipt of the positive charge is, I think, the essential process.

For, if the evidence given in this Journal and elsewhere be considered, it will be seen that the state of the colloids of the heart during inhibition is really an excitable state (1, 3, 4, 6). Excitation cannot take place, however, because the positive charge prevents the calcium from entering into the necessary combination with the colloids. The simple removal of this positive charge, such as occurs under experimental conditions, removes the condition preventing calcium from entering into its usual combination with the tissues, but does not immediately remove the 'state' of the heart to which it has also given rise. The subsidence of the 'state' shows hysteresis. It lags behind the agency producing it. The consequence is that we have the heart in an excitable state and now also capable of combining with the other factor producing excitation (3, 6). We have, in fact, the conditions for the 'inhibitory rebound' on which

are based the anabolic theories of inhibition associated more particularly with the names of Hering (8), Gaskell (7), and Verworn (11).

Another agency capable of producing a relative decalcification of the tissues together with an excitable state is sodium.   The resemblance of certain of its actions to inhibition and the 'inhibitory rebound' is given elsewhere (1). In a succeeding paper similar phenomena produced by other substances and capable of a similar explanation will be demonstrated (5).

The calcium tension of the perfusing solution has a special influence on inhibitory phenomena.   In accordance with what has been said previously on the rigidity of cardiac reaction in presence of solutions of high calcium tension (4), it may be also stated in general terms that the higher the calcium tension of the perfusing solution, the less readily does the heart show inhibitory phenomena. Not only is this the case, but, in a succeeding paper (5), the evidence will be presented that certain cardiac phenomena predominantly inhibitory become changed to phenomena predominantly excitatory when the balance of the elements of a perfusing solution is altered in the direction of producing a sufficiently greater tension of calcium.

Now, one of the consequences of a relatively greater tension of calcium in the perfusing solution must be the production of a relatively greater calcification of the tissues, and it is to this we must ultimately ascribe the changed reactions of those tissues.   We found above that the action of strychnine described there was compatible with the assumption that the tissue under its influence was able to take up more calcium from the perfusing solution than would be otherwise the case.   These drugs should thus enable us to reproduce some of the consequences that would otherwise arise from the use of a solution of higher calcium content. We may consider strychnine first.

There is something in the chemical nature of strychnine and something in the chemical nature of synapses which results in the effects of strychnine being concerned primarily with those synapses.   The consequences of its action are manifested as a facilitation of the passage across the synapses, and, as shown by Sherrington (10), by a capacity to change the process of inhibition to one of excitation.   Those consequences could follow on a relative calcification of the synapse. If the view of excitation put forward elsewhere be considered, we see at once there should be a facilitation of a propagated excitation (4).   In regard to inhibition further remarks are, perhaps, desirable.

If, as suggested, inhibition is essentially a decalcifying process, an inhibitory influence capable of decalcifying a normal tissue might well leave some calcium remaining on the same tissue under the changed conditions suggested above. The inhibitory influence, however, also alters the state of the heart in the direction of an increased excitable capacity (4, 9).   The amount of calcium left behind may, then, be sufficient to excite this tissue in its 'state' of increased excitable capacity.   We strike, as it were, the combination of the two factors of excitability, calcium and the 'state' of the tissue, adequate to produce an excitation (3, 6).   It is some such process as this, presumably, which underlies

the change from inhibition to excitation taking place under the influence of strychnine (10).

A similar action presumably underlies the same phenomenon as evoked by tetanus toxin. But in this case we have to deal with a poison with two stages in its action. It first of all enters into combination with a particular tissue and then changes its chemical composition. This specificity and twofold action combine to render its treatment so difficult. We have a specific antidote to prevent that primary combination, but we have no specific for the second. The symptoms depend on a chemical change following on the original combination. Had we a drug as specific in its action on the central nervous system as is tetanus toxin, but producing contrary effects, we should probably have more success in its treatment. As it is, once the change is produced, we can only combat its manifestations by agents producing physical rather than chemical changes, and with those same changes more general than the agency which they are required to combat. Owing to the specific chemical change underlying the symptoms, it is also quite possible that a form of treatment which, regarded from the standpoint of its effects upon a normal individual, would appear as highly dangerous, might be of actual benefit under the changed set of circumstances.

The change from inhibition to excitation considered above was there regarded as a later stage in a process hindering inhibition. The earlier stage of simple antagonism is apparently elicited by the agency of atropin. It is quite true that excitatory effects frequently follow attempted inhibition of atropinized hearts, but they are apparently due to actual accelerator fibres.

The action of ergotoxin is exerted primarily on the uterus. The peculiarities of its action are also explicable on the same lines as those before. The normal relation of the pregnant uterus to its perfusing solution is such that feeble peristaltic activity is the rule until parturition comes, when it becomes changed to a series of strong contractions. Elsewhere I have given an example of feeble peristaltic contractions of the heart being changed into strong forcible contractions by increasing the calcium content of the perfusing solution (2). The organs of the body, however, are perfused with a solution of relatively constant composition, and changes in their behaviour depend primarily upon changes taking place within themselves. Ergotoxin produces its change in uterine behaviour—presumably by causing some element of it to take up calcium from the perfusing solution. Three other ecbolic drugs examined by me were found to produce an increase of the cardiac response to calcium, so that they presumably act by altering the response of some part of the uterus to calcium.

The mode of action suggested for ergotoxin and its dangers are readily brought into line with the theories of excitation and inhibition already advanced. Following Macdonald, they presented inhibition as a prolongation and exaggeration of the process concerned in the normal reversal of systole, the process reversing a normal systole being a fleeting inhibitory process.

Ergotoxin by rendering certain uterine tissues capable of taking up more calcium from the blood will cause the appearance of a contraction where

otherwise one would not appear, but at the same time it acts adversely to influences tending to reverse that contraction. That is to say, we should use it when contraction without relaxation is desired. Its action in producing spasm of certain peripheral arterioles is presumably the result of a similar mechanism.

Thus, we have taken three different drugs and found them to have a common action on the heart capable of a particular explanation. Accepting that explanation, there were next shown the possibilities of variation of cardiac behaviour capable of production under such circumstances. Then, making allowances for the specificity of action of these drugs on the various tissues and on different phases of the cycle of contraction and relaxation, we find a whole series of effects brought into line with the fundamentals of the machinery of excitation and contraction, and revealing themselves, like the cardiac reserve, as alterations in the relations between the excitable tissue and its perfusing solution.

Summary.

1. A certain action is described as produced by strychnine, atropin, and ergotoxin in a certain type of abnormal heart.

2. From the conditions governing the production of this abnormality, and the conditions governing its removal, it is concluded that the particular effect produced by these drugs follows on an ability on their part to cause a degree of relative calcification of the tissues. Tissues brought under the influence of these drugs take up more calcium from the perfusing solution than would otherwise be the case.

3. The possible consequences of such a change are then examined by reference to the effects which follow on perfusion of solutions of relatively high calcium tension.

4. The changes so produced as described as varying from a change of inhibition to excitation, to the induction of tonic contraction.

5. By making allowances for the specificity of action of these drugs on different tissues, and the physiological differences between the tissues themselves, a whole series of effects are revealed as due to alterations in the relations between the excitable tissue and its perfusing solution.

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DESCRIPTION OF PLATE.

PLATE 21.   The perfusing solution contained —

$$
\left.
\begin{array}{lll}
0.6 & \text{per cent.} & \text{NaCl} \\
0.03 & ,, \quad ,, & \text{KCl} \\
0.01 & ,, \quad ,, & \text{NaHCO}_3 \\
0.0025 & ,, \quad ,, & \text{CaCl}_2
\end{array}
\right\} = \tfrac{1}{10}\ \text{R}.
$$

0.001 Str SO$_4$ = addition of 0.001 per cent. of strychnine sulphate to the above.

RESEARCHES ON THE PERFUSED HEART

SOME ACTIONS OF ADRENIN TOGETHER WITH SOME REMARKS ON ADDISON'S DISEASE

By W. BURRIDGE

(From the Physiological Laboratory, Oxford, and Guy's Hospital, London)

With Plates 21-25

THE well-known researches of Langley (18), Brodie and Dixon (4), Elliott (13), and others, have shown that adrenin is a drug capable of exciting in an organ the activities normally associated with excitation of sympathetic nerves. It has also been suggested by Howell and Duke (17) that the sympathetic nerves of the heart produce their effects by releasing calcium salts at their termination. The theory is based on their discovery that a sudden increase in the calcium content of a solution perfusing the heart may be followed by effects simulating sympathetic stimulation.

Certain objections may be raised against this theory. Inasmuch as the addition of calcium to the perfusing solution gives effects simulating sympathetic stimulation, it would follow that such perfused calcium salts penetrate to those structures where, according to the theory, excitation of sympathetic nerves releases calcium, and also that such released calcium can diffuse into the blood stream. But there is good evidence that sympathetic nerves exercise a tonic influence on the heart, and it is difficult to imagine them continuously releasing calcium salts. Moreover, the stimulating action which follows an increase of the calcium content of a perfusing solution disappears almost immediately after the calcium content is reduced once more to normal, and in addition a depressed state of the heart is left behind (6); whereas the effects following stimulation of sympathetic nerves persist some time after cessation of stimulation and we have not the depression.

Underlying this suggestion of Howell and Duke appears to be an assumption of a constancy of action produced by a given tension of calcium. I have given an abundance of evidence here and elsewhere (5–10), however, indicating that such a view is untenable. The magnitude of the cardiac response to calcium is an ever-varying value, and according to the nature of that response so calcium produces different results. This knowledge enables the suggestion to be

put forward that during sympathetic stimulation there is a change in the response of the heart to calcium, the change being that of an augmentation. Such a mechanism presents sympathetic stimulation as inducing a change in the response of the heart to its immediate and constant environment rather than as an autogenous change of environment reacting on the heart itself, as suggested by Howell and Duke.

Some evidence for this suggestion is given in the present paper, together with an account of other experiments which, it is believed, throw some light on the pathology of Addison's disease. The actual material of the paper will be found capable of a rough division into three main parts. In the first of these certain relations between adrenin and calcium salts are considered, and they show that adrenin may be regarded as a device enabling the organism to carry out certain functions in presence of less calcium than would otherwise be necessary. Some possible advantages of such a system have been discussed in an earlier paper (10).

The second portion of this paper deals with the action of adrenin whereby it enables cardiac activity to be maintained over long periods of time when the heart is perfused with solutions showing a decided lack of 'balance' between their inorganic elements. It is shown that the 'balance' between the inorganic elements of a perfusing solution acquires a secondary importance, so far as the mere maintenance of cardiac activity is concerned, when traces of adrenin are also present.

The third portion deals with certain changes constantly observed when Ringer's solution is substituted for blood as a perfusing medium, and with their interpretation. The latter provides also a convenient explanation of the origin of certain symptoms of Addison's disease.

Method of Experiment.

The experiments have been carried out on the hearts of *Rana temporaria* perfused *in situ* through a cannula inserted into the inferior vena cava, as already described.

The adrenin preparations used were the adrenalin hydrochloride solution prepared by the Parke Davis Co., hemisine and tabloid suprarenal extract prepared by Messrs. Burroughs and Wellcome.

Results.

The fluctuations in the level of the summation line which follow the addition of adrenin to a solution perfusing the faradized heart may be described first. An illustration of the change is given in Plate 21, Fig. 1.

On faradizing a heart perfused with Ringer's solution the heart enters

into a fluctuating semi-contracted state.   The contractions evoked by the
faradism usually start from a line, the summation line, situated at a higher
level than the line, the base line, whence start the spontaneous contractions (8).

A moderate dose of adrenin first quickly depressed and then gradually
raised this summation line; a strong dose (1 pt. in 25,000, say) depressed it;
the weaker doses (1 in 1,000,000, say) had no particular action, or slightly
raised it.

An experiment such as that shown in the figure above is quickly and
easily performed and has the great advantage of providing a directing post for
subsequent work.   Thus, having obtained that primary depression shown in the
figure, experience has shown me there will be a 'surface' (7) antagonism
between calcium and the substance producing that depression.   But to show
that antagonism it may be necessary to make a selection of both perfusing
solution and of concentration of drug.   An appropriate selection is shown in
Fig. 2.

From the arrow on the left of the tracing to the extreme right the perfusing
solutions contained 1 part in 25,000 of the Parke Davis adrenalin hydrochloride.
On the extreme left the heart was perfused with a Ringer in which the calcium
concentration was represented by one-fifth saturation with the dibasic phosphate
of calcium.   The condition of the heart at the commencement of the experiment
was such that it was beating well on this solution.   Incidentally, it may be
remarked that a capacity for beating well on that solution, apart from experi-
mental interference with drugs, may be taken as good evidence that the heart
was 'fresh'.   The perfused heart quickly loses its response to calcium, sufficient
to permit of good activity on that solution.

After addition of the adrenalin to that solution the beats of the heart
quickly fell away, but were restored again when the calcium content of the solu-
tion was increased to full saturation.   The experiment was repeated three times,
the degree of failure being permitted to proceed further on each new occasion,
until on the third occasion the beats became almost imperceptible.

A few remarks on the two solutions used above would not be out of place
here.   The solution of lower calcium concentration was not one that would
conventionally be regarded as a 'good' perfusing solution.   The usual test of
a good saline perfusing solution is to note how long a heart beats when perfused
with it.   The longer the heart maintains activity, the better the perfusing solu-
tion.   The conclusion is so obvious as to be almost a self-evident proposition.
Yet it will be found that different observers recommend different solutions, and
that not a few as a preliminary to other work find out for themselves what is
the 'best' solution.

If, however, the experimenter considers that an inorganic saline perfusing
solution is a makeshift device, as to which evidence is given later, a different
course is open to him.   My own method is to use a number of different per-
fusing solutions constant in composition except as regards the calcium content,
to ascertain the maximum contractibility of the heart, and to test its 'state' at

intervals.   The advantages of the method as they appear to me may be brought out by a mechanical metaphor.   The experimenter works with a machine of known maximum horse-power, he knows what proportion of that maximum is being given out at a particular moment, and he knows the state of the throttle required to elicit it, whereas the other method provides him with a machine of unknown horse-power and a fixed throttle.   With the latter method, although he may be conscious that the machine at a particular moment is not working as well as it did at some previous time, he cannot properly appreciate that depression.

In the case above, the sole use of the solution of higher calcium content, the 'good' perfusing solution, would have revealed a depression of the summation line in the faradized heart, but no corresponding depression of the spontaneous contractions.

The state of the heart at the time the experiment was made was also of importance.   The more responsive the heart was to calcium, the less readily was it depressed by adrenin.   There are, thus, three factors in this depressing action of adrenin, viz.: (1) The concentration of the drug; (2) the concentration of the calcium in the perfusing solution; and (3) the condition of the heart at the time of the experiment.

This depressive action of adrenin was exhibited in varying degrees according to the particular combination present of the conditions determining its appearance.   What is possibly of importance in connexion with it is the fact that actual concentration of drug is only one of the three factors concerned.   The higher the concentration of drug used the more likely is it to produce this depression, so that it is a drug which should not be pushed too hard.   The experiments also indicate the possibility that a dose of the drug which would stimulate a normal individual might have untoward consequences in an emergency.

An inhibitory action of suprarenal extract was noticed by Langley (18) and by Oliver and Schäfer (21), the first of these also observing the action after section of the vagi.   The depressive action of adrenin described above shows many resemblances to inhibition not only when the drug was actually present, but also in the 'rebound' to augmented activity observed subsequently and described below.   It is, I think, a truly inhibitory action, but its discussion is, perhaps, best left to a later period, where it can be considered in connexion with the augmenting action of adrenin to be immediately described.

The augmenting, or sympathomimetic, action (2) of adrenin corresponds to the secondary raising of the summation line observed when adrenin is perfused through the faradized heart.   But here again it was a question of getting the appropriate combination of drug and perfusing solution for its proper manifestation.   In my experiments the augmenting action of adrenin followed the depressing action whenever the latter was also shown.   One limit of experimenting was reached when the adrenin was used in quantities sufficient to stop the heart in diastole such has already been described.   In such cases when the adrenin was washed out of the heart the latter not only recovered its ability to

beat spontaneously, but it now beat much better than was the case before the exposure to adrenin.   The beats were now quicker in rate and of increased amplitude as compared with what they had been before treatment with the adrenin, the improvement persisting some little time, after which the heart gradually returned to the normal.

The relatively large dose of adrenin has, then, a twofold action on the heart.   There is a depressing action which comes on and goes away with addition to and abstraction from the perfusing solution of the adrenin ; and there is an exalting action which depends on previous contact of drug and heart, but does not then require the presence of the drug in the perfusing solution for its immediate manifestation.   From what has been stated in previous papers the depressing action of adrenin is a 'surface' action ; and its favouring influence on cardiac activity, a 'deep' action (7–10).

An examination of hearts during the period of exalted cardiac activity brought about by adrenin showed that during this period the heart had a greatly increased responsiveness to calcium as compared with what it had before treatment with the adrenin.   Both these actions are very well shown in Fig. 3.

It will be found instructive to compare Fig. 3 with Fig. 2.   In the latter the experiment shown was performed on a heart capable of beating well on a Ringer with a calcium content of one-fifth saturation with the dibasic phosphate.   In the experiment now considered, the heart, to beat well on a similar solution, required full saturation with the calcium salt as shown by the contractions recorded on the extreme left of the tracing, for on reducing the calcium content to one-fifth saturation the beats became very small.   When equilibrium to the new solution had just been established adrenalin hydrochloride was added to it (1 in 250,000).

Following the addition of the adrenalin to the solution there was a well-marked primary depression succeeded by a much greater augmentation.   The resemblance of that depression to inhibition is also well shown.   Later the adrenalin was removed from the perfusing solution, but it will be observed that the improvement persisted, and then the beats gradually fell away again.   About twenty minutes elapsed between removal of the adrenalin and the return of the heart to the condition existing before exposure to the drug.

The particular experiment illustrated above was one of a series performed on that heart.   In that series the heart was treated on each new occasion with a smaller dose of adrenalin than the one going before.   The experiments showed that a dilution of the adrenalin of 1 in 10,000,000 produced practically the same amount of augmentation as that shown above.   At a dilution of 1 in 50,000,000 the augmentation was about one-half that shown.   But with dilutions of 1 in 1,000,000 and upwards the primary depressing action was absent.   In experiments on other feebly beating hearts it was found that a dilution of 1 in 250,000 might not improve the beats, whereas a dilution of 1 in 1,000,000 did.   In general terms it may be stated that the more feeble the beats of

the heart, the less is the dose of this drug required to induce a primary depression.

Each suprarenal of normal adult cats has, according to Elliott (14), an average adrenin content of about 0·22 mg., so that, judged by these experiments, the sudden discharge of the whole of this into the animal's blood ought not to induce any decided primary cardiac depression. There is, however, the possibility that on the clinical side an endeavour to 'push' the drug might be followed by some such action. The existence of this primary depressing action indicates also a possible source of error in the use of adrenin to find the nature of the sympathetic supply to organs, for any action of the drug produced by large doses and not by small should be regarded with some suspicion. The action of the large dose will, of course, be an action of adrenin, but not necessarily that of sympathetic nerves.

As already stated, the sympathomimetic action of adrenin gives a cardiac state in which the heart has an increased responsiveness to calcium. The development of this state under the influence of adrenin is antagonized by calcium, for, as shown elsewhere, calcium induces a cardiac state unfavourable to its other actions. Thus, a sufficiently small concentration of adrenin added to a perfusing solution containing a sufficient concentration of calcium may show no definite sympathomimetic action, whereas that same dose of adrenin added to a similar perfusing solution, but of much smaller calcium content, gives distinct sympathomimetic effects. Or, the experimenter may desensitize the heart to calcium by calcium, as shown elsewhere (7), and then use adrenin to overcome the effects already produced by the calcium.

Antagonisms between calcium salts and certain actions of adrenin have already been shown by Schrank (24) and Frankl (15). In each of these instances a simple antagonism was found, but from the experiments above it will have been gathered that the antagonism between adrenin and calcium salts is compound in the case of the heart, and we may not unreasonably suspect that the same is true for other tissues. We have to take into account at least four factors made up of the two types of actions of each substance. Each of them exerts a 'surface' type of action, i.e. one which comes and goes respectively with addition to or removal of the modifying substance from the perfusing solution. These 'surface' actions of the two substances are mutually antagonistic.

Each of them also has a 'deep' cardiac action revealing itself as a change persisting after removal from the perfusing solution of the substance originally producing it, and in this also the two substances are mutual antagonizers.

There are thus two pairs of mutually antagonistic factors which we may set out as made up of—

(a) The concentration of the adrenin.

(a′) The concentration in calcium of the perfusing solution.

(b) The state of the heart induced by the adrenin.

(b′) The state of the heart induced by the calcium.

The immediately apparent result in any particular experiment depends on

which of these factors predominates. When the third factor predominates adrenin exercises a sympathomimetic action.

The understanding of these relations is quickly facilitated by a knowledge of the action of calcium in excitation processes. The bed-rock factor for consideration is the distinction that can be drawn between the working parts of the cardiac machinery and the accessories thereto (10). Excitation is a coagulative change evoked by calcium in certain colloids, and in the process we can distinguish two main factors, calcium tension and cardiac 'state' (9, 12), the latter being either electrical or physical, or both. Artificial or natural stimuli are to be regarded as agencies modifying this action of calcium. Bearing that in mind, there is no difficulty in visualizing the two mutually antagonistic actions of calcium itself, since we know that every efficient stimulus leaves behind it a refractory state.

The quicker an excitable organ overcomes or antagonizes the effects of a particular stimulus, the quicker does it become ready to respond again to a similar stimulus, so that adrenin, by antagonizing the refractory state produced by calcium, renders the heart also capable of responding more readily to the other actions of calcium. These antagonisms of 'state' between the two substances are those of chief interest from the physiological standpoint. The other antagonisms also have their interest, though they possibly play a relatively small part under normal conditions. The existence of these complex relations, however, gives scope for errors of interpretation in results. Those experimenters, for example, who only pushed the calcium, only found a single antagonism.

The Antagonism between Adrenin and Potassium Salts.

Frankl (15) found that adrenin was antagonized by potassium salts. The converse also appears to hold.

As is well known, the addition of potassium salts in moderate excess to a solution perfusing the heart is followed by a great slowing of the rate and general depression, ending finally in loss of electrical irritability.

The present experiments were performed in three main groups. In the one the calcium of the perfusing solution was present as the chloride and the chloride of potassium was added to it. In the others the calcium was present as the dibasic phosphate, and the potassium was added to this, either as chloride or as dibasic phosphate also. The amount of potassium added was usually sufficient to stop the heart in the dilated and electrically inexcitable condition.

The addition of adrenin to these perfusing solutions was followed by a return of electrical irritability and a resumption of spontaneous activity. The amplitude of the spontaneous contractions returned towards the value existing before the potassium salts were added to the perfusing solution, and might even surpass this if the amplitude on the original solution was distinctly less than the maximum possible for the heart. The return of excitability or the augmentation

of the amplitude of the spontaneous contraction in partially depressed hearts took place with great rapidity. A staircase action was observed, but the staircase was a steep one. At one moment the heart might be inexcitable to an induced shock, but two seconds later that same strength of stimulus elicited a good contraction.

On removing the adrenin from the perfusing solution, the heart continued to beat well for some little time longer, and then the condition of the heart appeared to be the same as that existing before the adrenin was added to the solution of extra potassium content.

If, however, the adrenin were not removed from the perfusing solution of the heart, it continued to beat in the presence of this extra potassium over long periods of time. The heart has been observed to continue beating with undiminished amplitude in presence of such amounts of potassium as were otherwise sufficient to stop it, for eight hours after the adrenin was added to the perfusing solution.

On removing the adrenin at the end of that time the heart reacted similarly to that observed when the adrenin solution had been perfused only a short time. The beats continued at the same amplitude for some time longer and then gradually diminished.

Some of the actions of adrenin are illustrated in Fig. 4 (A, B, and C).

In the illustrations to that figure there are first shown the effects which followed the addition of an excess of potassium to an otherwise adequate perfusing solution. The contractions rapidly fell away until they became just perceptible. Adrenalin hydrochloride was then added to the solution, with the result that the heart recovered its contractility and beat stronger than before. The second illustration, 4 B, shows the beats of the same heart nearly four hours after the addition of the adrenalin to the solution of increased potassium content. It will be observed that during this interval there had been no diminution at all in the amplitude of contraction. The adrenalin was now removed from the perfusing solution, with the result that shortly after there was again a rapid failure of the spontaneous contractions. But in this case it will be noted that the antagonizing action of the adrenalin outlasted its actual removal from the perfusing solution. That is to say, the antagonism depends on some cardiac state. After the failure following this removal of adrenalin from the perfusing solution it was again added thereto, with the result that the heart beat well again. It was beating equally well three hours later, when the experiment was discontinued.

The balance of the inorganic elements in the solution just considered was such as to render it in every sense of the word an unsuitable perfusing solution. The addition of the adrenalin to it altered matters entirely. One had now a good perfusing solution. When experimentation on that heart was concluded, perfusion had been in progress some nine hours. During that interval no food material of any kind was supplied. Yet there had been practically no diminution in cardiac activity after that lapse of time.

The perfusing solution considered above, regarded from the balance of its inorganic constituents, was unsuitable because of an excess of potassium. 'Unsuitable' perfusing solutions can also be constructed which owe their unsuitability to deficiency of one of the usual constituents. Be it understood that the term 'unsuitable' is employed here in a purely conventional sense as implying a mixture of inorganic salts on which hearts do not exhibit spontaneous activity for what is, again conventionally, a reasonable length of time. No rigid definition of these terms can be given, but their general sense will be understood from the remarks made above and below.

As an example of an 'unsuitable' perfusing solution, a Ringer with a calcium content represented by one-fifth saturation with the dibasic phosphate of calcium (= about 0·002 per cent. $CaCl_2$—Ringer's solution is usually made up with about ten times this amount). This solution has been met with earlier in this paper, and, as a variation, we will take here the modification of its ability to maintain cardiac activity induced by epinine. Epinine is a synthetic drug produced by Messrs. Burroughs and Wellcome, and is closely allied chemically to adrenin. It has a sympathomimetic action like adrenin (2) (Fig. 5).

The defects of the solution already considered above were chiefly due to the potassium being in excess ; the defects of the solution now under consideration are chiefly due to a relative preponderance of the influence of the sodium over the calcium. The evidence for this statement will not be given here, the question having been in great measure dealt with by me elsewhere (7).

The beats of a heart which had been perfused for $1\frac{1}{2}$ hours with this solution are represented on the extreme left of Fig. 5 A, and are there shown to be very feeble. On addition of epinine to the solution the beats greatly increased in amplitude, and on its removal they fell away again. Repetition of the experiment gave the same result. The epinine was added again to the solution and the whole perfused continuously for one hour. It will be observed that at the end of that interval the amplitude of the beats was undiminished (extreme left of Fig. 5 B).

The epinine was then removed from the perfusing solution, with the result that the beats fell away, to be restored again when the epinine was re-introduced. A second removal of the epinine was again performed, with the result that failure again began. But in this case the failure was interrupted by increasing the calcium content of the solution to full saturation with the dibasic phosphate. The great and rapid increase of contraction which thereupon took place was sufficient to show that all that was required to enable the heart to exhibit good activity in a purely saline medium was the addition of more calcium to the perfusing solution. Reduction of the calcium content to one-fifth saturation was followed by a rapid failure, which was overcome by the addition of epinine once more. Three hours later the amplitude of the beats was still maintained, when the experiment was discontinued. Incidentally, it is, perhaps, of some interest to compare the 'curve of failure' which ensued on removal of epinine

from the solution, and the diminution in calcium content.   Like adrenin, epinine favours cardiac activity by inducing 'deep' changes, whereas the favourable action of calcium is a 'surface' effect.   The 'curve of failure' following removal of epinine is concave to the base line, whereas that following removal of calcium is converse.

'Unsuitable' perfusing solutions were also constructed which owed their unsuitability to an excessive calcium content (0·05 per cent. to 0·2 per cent. $CaCl_2$). Here again adrenin made possible a great prolongation of activity.

Thus, taking as a test of the suitability of a perfusing solution the fact whether the heart can perform a satisfactory amount of work on that solution or not, we see that in presence of a trace of adrenin the 'balance' of the inorganic constituents becomes of secondary importance.   In presence of a trace of adrenin a badly 'balanced' solution becomes more efficient to maintain cardiac activity than is a 'well-balanced' solution without adrenin.

Some Differences between Blood and Saline Perfusing Solutions.

Subsequent to the original work of Ringer one of the objects of those who devised inorganic saline perfusing solutions was to obtain one which in its 'balance' between the different constituents should approximate to that of blood. It is reasonable to believe that the balance in blood approaches perfection, but, owing to the different proportions between 'sorption' and solution of the different salts, analyses of blood ash give little information as to this balance.   Of one particular salt, it may be that one part is in solution to three parts associated with colloids ; of another salt, the contrary relation may hold.   The result is that the only real test one can apply is that of comparing the results of cardiac activity on solutions of different composition.   It is so obvious that the longer a heart can maintain activity on a particular solution the better is that solution suited to cardiac activity, that there is apparently nothing to gainsay about it.

Yet it is possible to acquire some scepticism about these views by considering Addison's disease.   The symptoms of the disease originally described by Addison are now known to be almost identical with those arising after excision of the suprarenal bodies.   But, while agreeing that absence of the internal secretion of those bodies is a necessary antecedent to the actual appearance of the symptoms of this disease, it should at the same time be realized that the *causa causans* of those symptoms is to be sought in some peculiarity of the bodily mechanism. For some reason or other this mechanism minus the adrenal secretion is defective, and the symptoms of Addison's disease give us some measure of its defects. Inasmuch as the adrenal secretion is poured into the blood, it is possible that peculiarities in the composition of the latter may account for some, if not all, of the symptoms of Addison's disease.

That is the view which arises, I think, from the experiments below.   The preliminary proposition to be put forward is that Ringer's solution never has the balance of blood.

This view is based on certain differences of reaction which are *always* obtained when the base of the ventricle is faradized immediately before and immediately after blood is substituted by an inorganic saline perfusing fluid. The strength of current used is the strongest that can be employed in the frog's heart perfused *in situ* ; viz. one that caused feeble fibrillary twitchings of the pectoral muscles by spread, but without inducing any general contraction. If the strength of current be increased beyond this, the contractions of these muscles influence also the movements of the heart-recording lever.

Certain other precautions were taken. Thus, between the death of the animal and the procedure of replacing the blood in its heart by saline, there is the interval involved in the operations of inserting the cannula, fixing the heart to the recording lever, &c. To eliminate any possible error arising from this source, a number of experiments were performed on spinal frogs in which observations were made at intervals from two or three minutes to one hour after destruction of the cranial contents. No qualitative change took place.

By using a strength of current sufficient to cause fibrillations of the pectoral muscles when the electrodes were touching the base of the ventricle, the local cardiac nervous mechanism was also brought under its influence.

On application of the faradizing current to the base of the ventricle under these conditions, there was usually evoked a ventricular contraction of about the same amplitude, or slightly greater than that of the previous spontaneous contractions. This was quickly succeeded by a second smaller contraction and a third one barely perceptible. Thereafter the faradizing current evoked at irregular intervals contractions of irregular amplitude, but smaller in amplitude than those existing before faradizing. Sometimes beats regularly alternating in strength were present, at other times the heart remained quiescent.

No two hearts ever reacted similarly. The description above merely gives some of the outstanding features observed. There was an apparent anarchy in the results obtained.

The explanation of the anarchy is simple. The faradization excited both the ventricle and the local nervous mechanism, with the result that it became subject to mixed forces of inhibition and excitation. Inhibition always predominated in the blood-containing heart, and the anarchy of results was due to irregular partial breaks in this inhibition.

Directly after the blood in the heart had been replaced by any of the usual inorganic saline perfusing solutions, the reaction of the heart to the same faradizing current was radically changed. Inhibition disappeared, or at any rate gave no definite evidence of its existence. Instead the heart reacted to the faradizing current in a manner consonant with reasoning employed by Engelmann, viz. that by using a rapid faradizing current some one of the shocks will fall on the heart during diastole approximately at the point where the returning excitability associated with diastole renders the heart excitable to the strength of shock used. The contractions now evoked by the artificial stimulus came on so early in diastole that the heart was unable to relax completely. The

contractions evoked by the artificial stimulus also started from a different base line, the summation line, than that from which the spontaneous contractions started.   These artificially evoked contractions came on so much faster than before and frequently succeeded each other so quickly as to give almost complete fusion. Under certain conditions a condition resembling the tetanus of skeletal muscle could be obtained.   An example of the change taking place in the reaction of the heart to faradization on passing from blood to inorganic saline perfusing solution is given in Figs. 6 A and 6 B.

The type of change shown in the diagram was constantly obtained on passing from blood to an inorganic saline perfusing solution.   Several hundred experiments were made, and the perfusing solutions comprised all those recommended as suitable for the heart, and many others as well.   Provided the saline solution was one that enabled cardiac activity to be maintained for half an hour, it was also one incapable of allowing the heart to show those predominantly inhibitory phenomena seen immediately previous to its perfusion.   No matter how well a given inorganic saline mixture enabled a heart to maintain spontaneous activity, there was always that difference observed when it was substituted for blood as a perfusing solution.   There is something in the composition of these solutions which renders them vastly different from blood.

The immediate impression arising from these results is that inorganic saline perfusing solutions destroy the local inhibitory mechanism of the heart.   That is not so, however,' for predominantly inhibitory effects produced under the circumstances mentioned above in hearts perfused with inorganic saline mixtures after they had been treated with high concentrations of potassium salts (1–5 per cent.).   The return of inhibition under such circumstances was temporary and corresponded to the period of ' loading ' of the heart with potassium (5).   But it was sufficient to show that these perfusing solutions were unsuitable media for the manifestation of inhibition, rather than destroyers of the local inhibitory mechanism.   An example of such ' return ' is shown in Figs. 7 A–7 E.

Two other points about this change, and, I think, indicative of its nature, are : (1) It took place immediately after the salt solution was substituted for blood.   (2) The summation line was raised.

The former places the phenomenon in that group of actions I have termed surface actions (7).   Experiments performed in other directions show that a change in the relative proportions of the inorganic salts present would produce this. A change of state would probably take longer than the time interval elapsing in these experiments.   A change of state can be finally eliminated by the facts that the blood-containing heart is highly sensitive to calcium and gradually loses this sensitiveness when perfused.   The change actually shown is, thus, opposite to that shown by the heart on the assumption that the phenomena now considered were due to a change of ' state '.

A raising of the summation line is always produced in the perfused heart when either the response of the heart itself to calcium or the tension of the

càlcium in the perfusing solution is raised. But having already eliminated changes in ' state ', we are left with an increased tension of calcium as responsible for the change. The validity of the premises leading to this conclusion is enhanced by the fact that, using entirely different methods, Keith Lucas (19) has already demonstrated that Ringer's solution has a greater calcium tension than blood.

The changes taking place in the level of the summation line when the tension of calcium in a saline perfusing solution is increased are well shown in Plate 25, Figs. 8 A and 8 B.

This greater tension of calcium may either have been due to the perfusing solution containing an absolutely greater amount of calcium than blood or a relatively less amount of sodium or potassium.

We may at once deal with the sodium. The perfusing solutions contained 0·6 per cent. sodium chloride, which is isotonic with the red blood corpuscles of the frog. As shown by my former experiments, a diminution in the amount of sodium chloride would have led to a raising of the summation line immediately after the one solution was substituted for the other (7), (8). To attempt to account for the raising of the summation line in terms of a smaller content of these perfusing solutions in sodium chloride was thus impossible, because it meant the assumption that blood contained a greater tension of sodium chloride than that which is isotonic with it.

There was a difference in the reaction of the two solutions, the saline solution being more alkaline than blood. The difference was such as according to my previous experiments would raise the summation line, but not within the limits of time here considered. On the contrary, the effects observed should have been those of depression (8).

A series of experiments was then made in which the changes were observed on passing from blood to a series of solutions constant in composition except as regards their calcium content, each experiment being made on a separate heart. The basic solution contained 0·6 per cent. sodium chloride; 0·03 per cent. potassium chloride ; 0·01 per cent. sodium bicarbonate.

It was soon found that no mere reduction of calcium content of these solutions could make the summation line of the fresh heart coincide with the base line of the spontaneous contractions and leave the heart capable of maintaining functional activity. A point was always reached where the amplitude of contraction on passing from blood to perfusing solution made a sudden drop and then more slowly increased again towards its former value.

The reason of these variations in the amplitude of the spontaneous contractions is again made clear by former experiments. They were such as take place when the balance between sodium and calcium is disturbed in such a way as leaves the former preponderating over the latter (7).

The final element to be considered was potassium, and this apparently afforded the key to the problem. Phenomena of inhibition under the conditions mentioned above returned—

N 2

(a) After hearts had been treated with large doses of potassium salts.

(b) During the period of failure associated with the perfusion of solutions containing sufficient potassium to stop the heart in the dilated condition, or at any rate to depress greatly its activity.

The return of inhibition under the former condition was only temporary. But it was the only way in which I found it possible to obtain decided inhibitory phenomena by the method used in presence of a solution of inorganic salts alone capable of maintaining good cardiac activity. The dose of potassium had to be a large one (above 1 per cent.), and the inhibition was obtained at a time when, according to the evidence in a previous paper, the tissues could be considered as containing large amounts of potassium. A relative excess of potassium in the tissues thus seemed to be a factor favouring inhibition. This accords with the work of Bottazzi (3), Howell (16), Macdonald (20), and others.

But on attacking the problem the reverse way, namely, by using solutions containing more and more potassium, it was found that as the potassium content of the solutions was increased, so the phenomena obtained by the experimental method used tended to approximate nearer and nearer to those of inhibitory type. But they did not become definitely so until the amount of potassium added was such as markedly interfered with the activity of the heart.

The addition of adrenin to these solutions not only enabled the heart to maintain activity on them, but also to preserve some phenomena of inhibition. Thus, supposing the start was made with a saline solution on which the heart beat well, but on which it showed no evidence of inhibition under the experimental conditions; instead faradization evoked excitatory activity with a summation line about two-thirds as high as the summits of the recorded spontaneous contractions. On adding potassium to such a solution sufficient to stop the heart in the dilated condition, faradization of the heart elicited inhibitory phenomena during the period of failure. Then, on adding adrenin to this new mixture, it was easy to get the heart to beat as well as it had done previously before the addition of potassium. But the summation line lagged behind. Whereas previously it was raised, it was usually now at the same level as the base line. After replacing this mixture by the original saline solution, the same jump in the summation line took place as was the case on passing from blood to saline mixtures.

It would have been of interest, perhaps, to have discovered a saline perfusing solution on which the heart behaved *exactly* as it does on blood. The war and other circumstances have, however, stopped experiments for the present.

If, however, we consider the points established above—

1. That the frog's heart shows a radical change in its behaviour immediately after Ringer's solution is substituted for blood;

2. That this change of behaviour, loss of predominance of inhibition, is not due to destruction of the local inhibitory apparatus, but to Ringer's solution being an unsuitable medium for its manifestation;

3. That this unsuitability of Ringer's solution is due to its relatively greater calcium tension than blood ;

4. That the relatively greater calcium tension of Ringer's solution is due largely to an absolutely diminished potassium tension ;

5. That a loading of the heart with potassium temporarily brings back predominantly inhibitory phenomena ;

6. That traces of adrenin overcome the inhibitory action of certain perfusing solutions containing an excess of potassium less than their action on amplitude of contraction ;

we have, I think, a sufficient body of evidence to indicate the origin of certain symptoms of Addison's disease.

Much of the work done on the suprarenals, prior to that by Oliver and Schäfer (21), was directed towards showing that their secretion neutralized toxic bodies. The nature of these toxic bodies was unknown, but they induced definite symptoms such as muscular weakness, shown by Abelous and Langlois (1) to be localized to the nerve endings, cardiac feebleness, and low blood-pressure. The general tenor of these experiments and the views arising therefrom are well presented by Rolleston (23).

But with the discovery of adrenin there was discovered a positive entity producing definite physiological results and accordingly modifying views in regard to the action of the suprarenals.

The view arising from the present experiments is a sort of half-way house between these. Taking first of all the only possible test of the suitability of a perfusing solution, namely the relative capacity of the heart to maintain activity on it, we have seen that in presence of traces of adrenin the balance between the inorganic constituents becomes of secondary importance. Varying extremes of unsuitability due to lack of ‘ balance ’ between the inorganic constituents were taken, and it was shown that the addition of traces of adrenin to these solutions rendered them better than the best balanced inorganic salt solution in their capacity for maintaining cardiac activity. Comparing next certain activities of the blood-containing and the perfused heart, it was shown that the behaviour of the blood-containing heart never approximated to that of the heart perfused with a ‘ well-balanced ’ inorganic mixture. Approximation of behaviour only began when the inorganic mixture became overbalanced in a certain direction.

Now, we have every reason for believing that adrenin is a normal constituent of blood. We also know that certain defects arise with its absence from blood. From the experiments above we saw that in presence of traces of adrenin ‘ balance ’ between the inorganic constituents of a perfusing solution becomes of secondary importance. They indicated also that blood is an ‘ unbalanced ’ solution in which the action of potassium predominates. Of the action of such a solution we have some knowledge. It enfeebles cardiac action, decreases vascular tone, and renders muscle easily fatigued. We have not the same knowledge in regard to its action on the skin, gastro-intestinal system, &c. But, where we have the knowledge, the action corresponds to the symptoms of Addison's disease.

Concluding Remarks.

The material of the paper will have been found to divide itself conveniently into three main parts. The first of these dealt with the relations between calcium and adrenin, and is the one to which further attention will now be given. The relations found were those of a mutual antagonism and reinforcement. They give a good illustration of the principle laid down before that the temperament of an organ depends on the calcium content of the solution perfusing it (10). In the present case we have a substance exerting a depressing and an augmenting action on the heart, each of which is antagonized by the calcium, so that whichever of these actions adrenin tends to exert at a given moment, its realization is rendered more difficult or more easy according as calcium is also present in greater or less amounts.

Regarding the results from a more general standpoint, we see in adrenin a device for enabling the organism to carry out its functions on a solution containing less amounts of calcium than would otherwise be necessary, and *ipso facto* endowing it with a greater power of reacting to its environment.

It is also of some interest to consider the relations between the augmentive and the depressive actions of adrenin. When small doses of the substance were employed the effects found were such as could be ascribed to sympathetic stimulation, whereas the large doses gave 'inhibition' and 'inhibitory rebound'. There was, however, no dividing line found between these two apparently diametrically opposite actions, but instead the one action gradually merged into the other. The possibility then arises that both these actions represent different aspects of certain fundamental effects of the drug. That such is the case is rendered possible by the grading effects shown in these experiments, and on the theoretical side they have a ready explanation in certain theories of excitation and inhibition already advanced (10, 11).

Modifying Macdonald's theory, I have suggested that in excitation there is a coagulative change in certain colloids through formation of a calcium compound (10). According to him this coagulative change is accompanied by a release into watery solution of previously absorbed potassium salts which now confer a positive charge on the colloids whence they came. This electric charge in its turn reverses the coagulative change in the colloids and so brings conditions back towards the original state of affairs. During inhibition Macdonald (20) considers that a maintained positive charge produces a finer state of colloidal subdivision than normal with a coincident withdrawal of more potassium salts from watery solution. I have shown, however, that a positive charge renders the cardiac colloids incapable of combining with calcium and can decalcify them as well as does an oxalate (6), and also that sodium may be a factor in determining a finer state of subdivision of the colloids (7). Modifying Macdonald's theory in accordance with this action of the positive charge, one sees as a prime factor in inhibition an inability on the part of the inhibited tissue to combine with calcium. The state of aggregation is of secondary importance, and

is indeed one which greatly favours the action of calcium. Both views, however, present inhibition and diastole as resulting from the action of a single agency. Diastole is an inhibition of systole, and inhibition itself an exaggeration of the action producing diastole.

Now, we know that the heart is normally quickened at the expense of the diastolic period, and that adrenin is a substance which quickens the diastolic process. The inhibitory action of adrenin is explicable on the assumption that it depresses the capacity of calcium to combine with the cardiac colloids, and its sympathomimetic action is explicable on the assumption that it produces a state of the heart the opposite of the coagulative. If the excited and therefore non-excitable heart be one in which there is a coagulative change resulting from the formation of a calcium-colloid compound, both these actions of adrenin should hasten its reversal. If, however, we consider the series of experiments performed on one heart, in which the degree of improvement following exposure to successively decreasing doses of adrenalin was noted, and draw a curve by plotting improvement against concentration of adrenalin, the curve becomes flattened after concentrations of one part in ten millions. That concentration presumably represents what was the maximum dose giving improvement in that heart consistent with economy of drug. It may be regarded as the counterpart of an oxygen tension of 150 mm. Hg in its relation to blood. At that tension blood is practically saturated with oxygen. It can take up more oxygen if the oxygen tension be increased further, but the amount so taken up is now very small relative to any such increase. Similarly the drug at the concentration mentioned had nearly reached its maximum as regards producing an excitable state. Pushing the drug further had little further action in this direction. Its decalcifying action did not, however, have a similar limit, so that with this further pushing of the drug it tended to predominate. When it was paramount, a heart was obtained in a highly excitable 'state', but incapable of being excited on account of its incapacity to combine with calcium. On removing the adrenin, the agency rendering the heart incapable of combining with calcium was also removed, but not the 'state' of the heart induced by the same agency. The latter took some further time to subside, and during that time we had the 'inhibitory rebound' to augmented activity which was found to be similar to the visible sympathomimetic action of the drug.

Thus, adrenin appears as a substance exerting two fundamental actions on the heart, each of which has a different maximum. The visible effects of these actions depend on the adjustment between them. I would not claim that the adjustments I have obtained between them are other than coarse. The body probably attains a finer adjustment and with it further refinements of its action, and so produces augmentive, accelerator, or initiative effects as they are necessary. There may be in the sympathetic nerve fibres mediating each of these effects, but from what has been stated above we see the possibility of such effects resulting from a grading of the adjustment between two fundamental actions of these nerves.

Addendum on Epinine.

Epinine is a substance prepared by Messrs. Burroughs & Wellcome. It is closely allied to adrenin, differing from the latter only in the absence of the alcoholic hydroxyl group in the side chain. First synthesized by Pyman (22), its physiological action was shown by Barger and Dale (3) to approximate very closely to that of adrenin.

In regard to its sympathomimetic action, all that has been said above holds good for epinine, one of the illustrations there concerning perfusing solutions showing this action of epinine. The action of this substance, thus, bears out what has already been said in this paper.

Like adrenin it can also exert a depressing action on the heart when used in large doses. This depressing action, however, is unlike anything else I have met. Thus, I used a strength of epinine of one in twenty-five thousand and perfused it in a Ringer solution one-fifth saturated with calcium phosphate. The heart began to fail though rather slowly. Before failure had gone far the epinine was removed from the solution, but the failure went on in spite of the removal. It was traced as continuing progressively during a further period of ten minutes by means of solutions of increasing calcium content. After the failure on the solution mentioned above, the heart beat well on a solution fully saturated with the calcium phosphate, but then failed again. A Ringer containing 0·025 per cent. $Ca Cl_2$ was next employed and with a similar result. After that a solution containing 0·15 per cent. $Ca Cl_2$ was used, also with a similar result. With each new solution of higher calcium content than that previously used there was a fresh outburst of activity followed by a failure.

At the end of that series the contractility of the heart as estimated by potassium chloride was found undiminished. But on evoking a series of such contractions it was next found that these also diminished in amplitude in succession. In some cases potassium salts ceased eventually to produce contraction.

The action was, however, in some measure reversible because with continued perfusion of the Ringer's solution contractility to potassium chloride and excitability to induced shocks began to return. After 1 in 5,000 epinine at least one hour elapsed between the original failure and the subsequent visible return of spontaneous contractility. But on the latter solution a 50 per cent. return only was obtained.

In other experiments the failure was not carried out to the extent mentioned above. The process could not be rigidly controlled, but it was found possible to render the heart incapable of beating well on a particular solution, but capable of beating well on a similar solution but of higher calcium content. Thus, a heart beating well on a Ringer solution containing 0·05 per cent. calcium chloride ceased spontaneous activity when 1 in 250,000 of epinine was added thereto, and did nòt resume activity when the epinine alone was removed. But

it immediately resumed activity when the calcium content of the solution was increased to 0·025 per cent.

The conclusion established from these experiments, that epinine used in the strength and under the circumstances mentioned above desensitizes the heart to calcium, was confirmed by using adrenin. Hearts perfused with a particular solution and rendered completely inexcitable to induced shocks as a result of treating them with epinine, could have that excitability restored by appropriate addition of adrenin to the same solution.

Now, if any particular change induced by epinine was due primarily to chemical changes we ought to enhance that change by increasing the epinine concentration. The evidence, such as it is, indicates that the 'epinine-heart' compound is unsuitable to show the normal activity. If, however, we take the view that the state of aggregation of certain cardiac colloids is a factor determining the outward manifestations of its activity, a physical change induced by a given drug can be regarded as sufficient to influence such activity. The indication is that sympathomimetic actions are primarily the result of physical rather than chemical changes.

The experiments are also of interest in demonstrating the delicate adjustment of the animal organism to its own drugs. Epinine and adrenin have similar physiological effects, but when we employ them in what may be considered as pathological concentration we get evidence of a certain lack of adaptation of the tissues to an environment containing epinine. It is conceivable that causes originally leading to the animal synthesis of adrenin produced also allied bodies, but evolution is behind the present adaptation to adrenin, and it seems possible that it represents a survival of the fittest.

Summary.

1. Adrenin has a twofold action on the frog's heart, a primary depressing action resembling inhibition, and an augmenting action, the sympathomimetic action.

2. Three factors are found to be concerned in the depressing action of adrenin.

3. The relations between adrenin and calcium are found to be fourfold.

4. The evidence is given that traces of adrenin render 'balance' between the constituents of an inorganic saline perfusing solution of secondary importance in regard to their suitability as media for the manifestation of cardiac activity.

5. It is shown that the behaviour of a heart perfused with a 'well-balanced' Ringer's solution never approximates to the behaviour of the blood-containing heart and that the change takes place immediately after the one solution replaces the other.

6. It is shown that as inorganic perfusing solutions become unbalanced in a certain direction, so the behaviour of the heart on them tends to approximate to that of the blood-containing heart.

7. Such solutions contained amounts of potassium sufficient to interfere with cardiac activity.

8. Traces of adrenin rendered them capable of maintaining cardiac activity and of preserving in great measure the resemblances between the behaviour of the heart perfused with them and of the heart containing blood.

9. On the basis of these experiments it is suggested that the proportions between the inorganic constituents of blood are such as to render it an unsuitable medium for the manifestation of cardiac activity except in presence of adrenin. The origin of certain symptoms of Addison's disease is traced to such lack of balance.

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DESCRIPTION OF FIGURES.

PLATE 21, FIG. 1.   Heart faradized between the signs + and ↑.

At ↘ 1/20,000 Adr. one part in 20,000 of the Parke Davis preparation perfused.

This was perfused at high pressure to overcome the resistance of the partially contracted heart.   The first sudden rise of the summation line is due to this sudden rise of perfusion pressure (*Pr.*).

At *Po* the perfusion pressure was reduced to normal and summation line fell slightly in consequence.

FIG. 2.   From the first arrow on the left to the extreme right the heart was subjected to solutions containing 1 in 25,000 adrenalin hydrochloride.

At ↑ $\frac{1}{5}$ the calcium content of the solution was that of one-fifth saturation with the dibasic phosphate.

At ↑ 1 the calcium content was that of full saturation.

Here and elsewhere CaHP signifies a perfusing solution containing 0·6 per cent. NaCl, 0·03 KCl and saturated with the dibasic phosphate of calcium.   A fraction sign in front, e.g. $\frac{1}{5}$ CaHP, indicates a similar solution, but with its calcium content reduced according to the fraction.

PLATE 22, FIG. 3.   On the extreme left the heart was beating on a solution fully saturated with the dibasic phosphate of calcium.

At ↘ $\frac{1}{5}$ CaHP the calcium content was reduced to one-fifth saturation.

At +1 in 250,000 that strength of adrenalin hydrochloride was added to above.

↘ $\frac{1}{5}$ CaHP = that solution without adrenalin perfused.

FIG. 4 A.   On extreme left heart was beating on a solution saturated with the dibasic phosphate of calcium.   The failure there seen is due to the addition of 0·05 per cent. of the dibasic phosphate of potassium (+0·05 K_2P).

At +1 in 1,000,000 Adr. perfusing solution made up to that strength in adrenalin hydrochloride.

1·15 represents time of day.

FIG. 4 B.   Beats some four hours after A.

↘ Adr. off.   Adrenalin removed from the perfusing solution.

↘ +1 in 1,000,000 Adr.   Adrenalin replaced.

Note that although four hours had elapsed between taking the tracings of beats on the extreme right of both figures there has been no measurable reduction in amplitude.   Perfused with a 'well-balanced' Ringer alone, the frog's heart would show a 25–50 per cent. reduction in a similar time.

PLATE 23, FIG. 5 A.   The feeble beats seen on the extreme left represent what would be 'normal' amplitude for a heart perfused with the $\frac{1}{5}$ CaHP solution after the time which had here elapsed since perfusion had been begun.   The waxing and wanings seen represent the effects following addition of epinine to that solution and its subsequent removal.   The 'breaks' in the tracings taken on the slow-moving drum are artificial, and are usually the result of floor vibrations.

FIG. 5 B.   The epinine introduced at 3.50 p.m. (see 5 A) was removed at 4.50.   There was, however, no measurable diminution in amplitude during that interval.   The remainder of the tracing is devoted to showing—

(1) That epinine was necessary for activity on the $\frac{1}{5}$ CaHP solution ;

(2) That the beats were feeble on the $\frac{1}{5}$ CaHP solution, because of its small calcium content—perfusion of CaHP solution.

See also remarks in text.

FIG. 6 A.   The base of the ventricle was faradized between the marks + and ↑.

Up to the white square the heart contained blood.   At the white square the blood was expelled from the heart and replaced by a saline perfusing solution.   The irregularities *P. V.* are the result of manipulation.

Immediately after replacing blood by the saline perfusing medium faradism evokes a condition resembling tetanus.

Note.—The perfusing solution used here was specially selected as giving an exaggeration of the effects usually seen, since here the change is from inhibition to tetanus approximately. The reaction on the usual Ringer is shown in Figs. 1, 7, 8.

Strychnine   FIG 1

Adrenin   FIG. 1

FIG. 2

Fig. 3
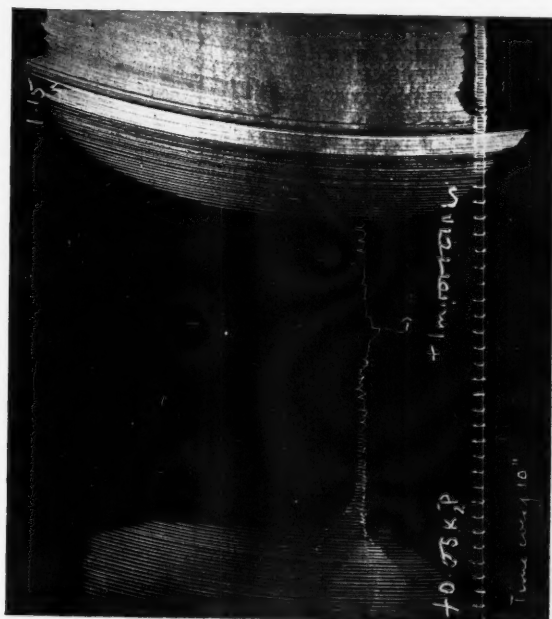
Fig. 4 B

Fig. 4 A
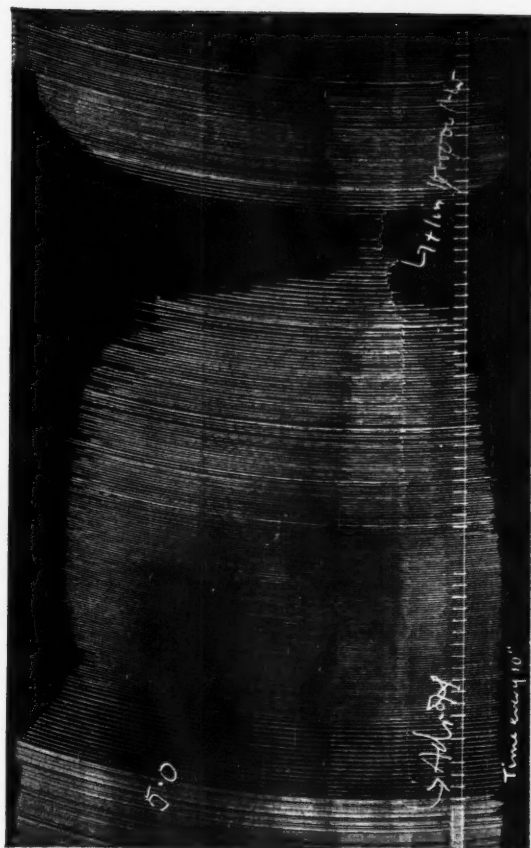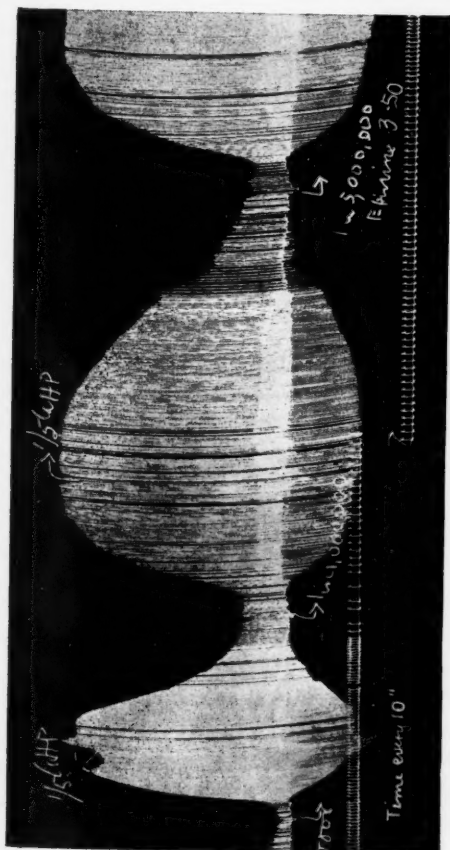
FIG. 5 B

FIG. 6 B

FIG. 5 A
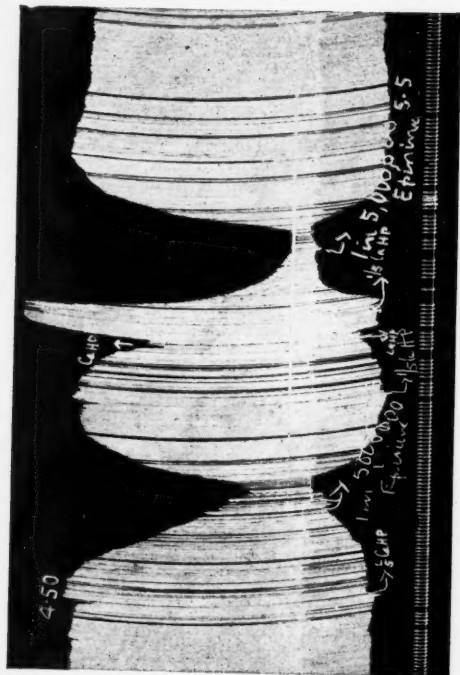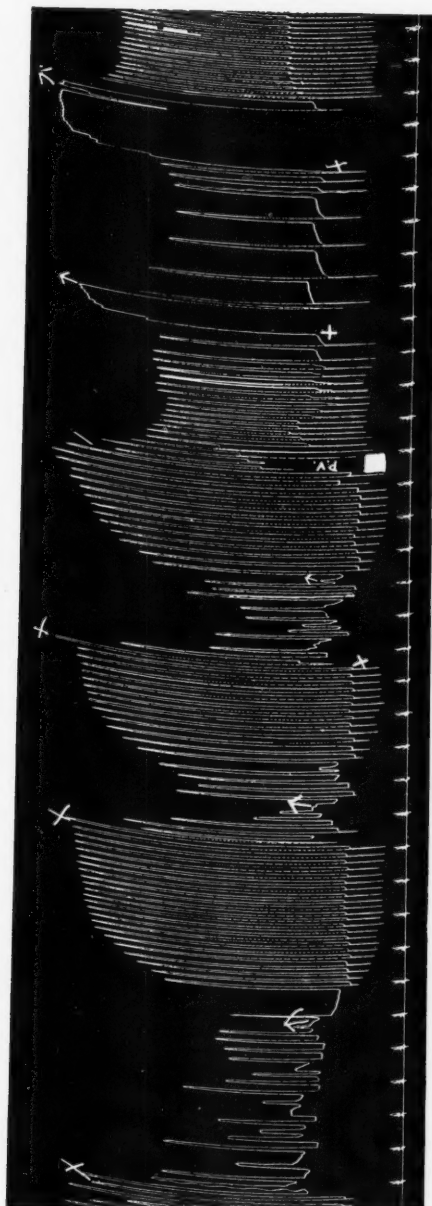
FIG. 6 A
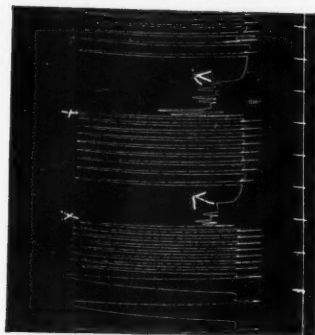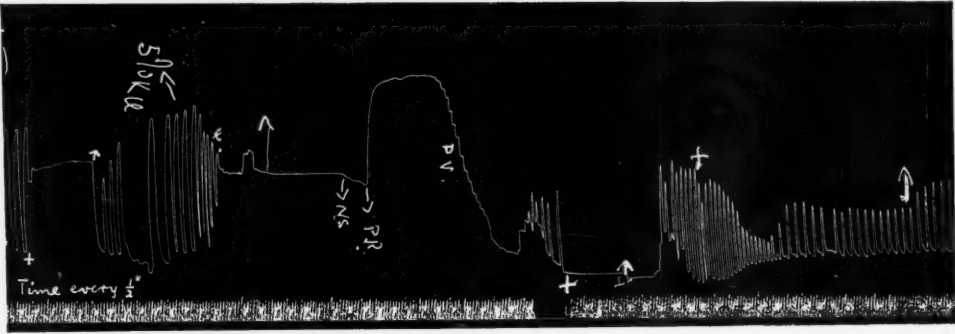
FIG. 7 A
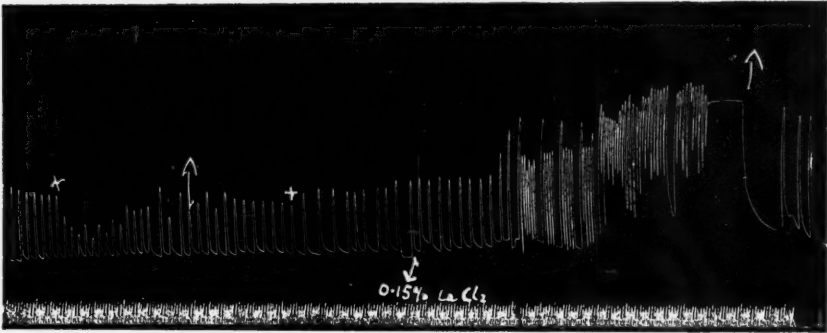
FIG. 7 B

FIG. 7 C
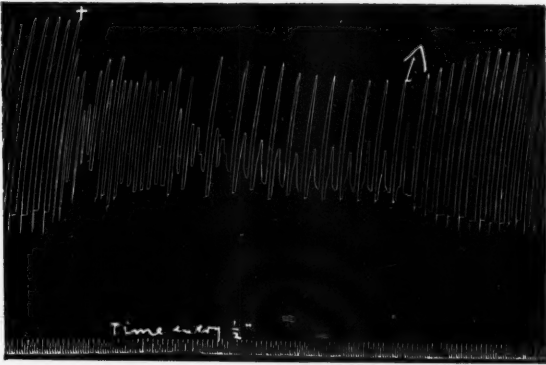
FIG. 7 D
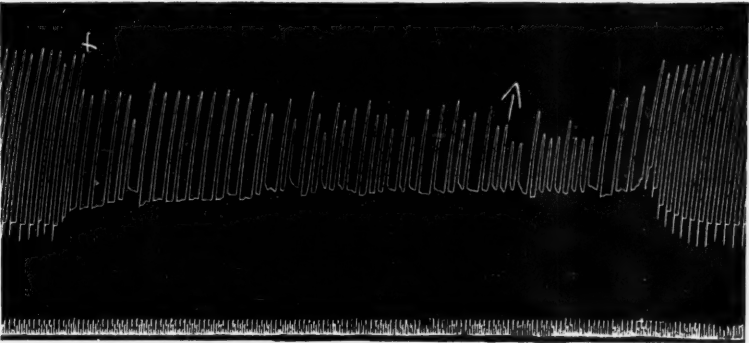
FIG. 7 E
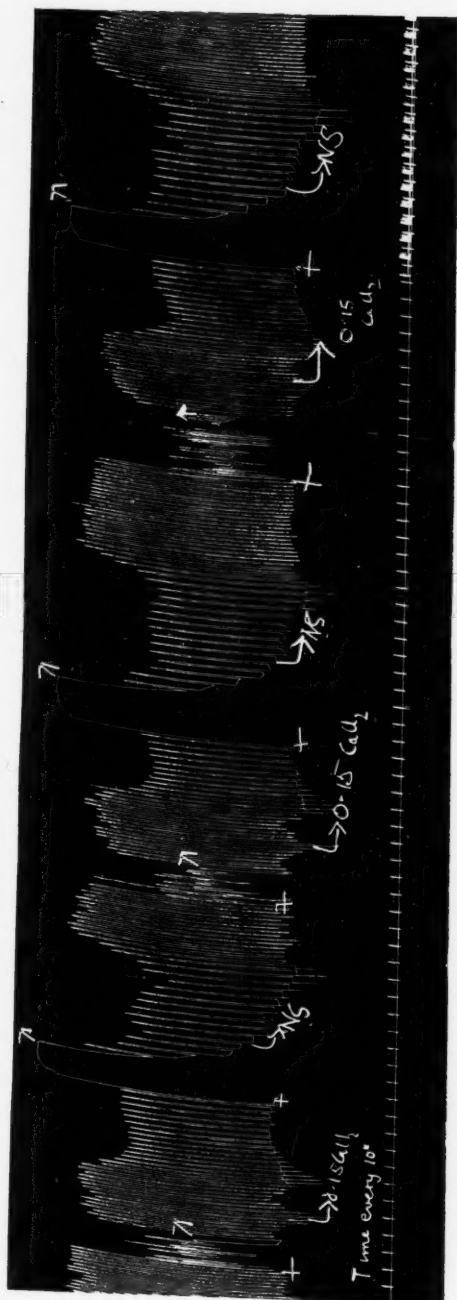
FIG. 8 A

FIG. 8 B

PATHOLOGY OF DYSENTERY IN THE MEDITERRANEAN EXPEDITIONARY FORCE, 1915

By G. B. BARTLETT

From the Pathological Institute of the London Hospital

(*Report to the Medical Research Committee.*)

With Plates 26–34

Contents.

PART I. SOURCE OF MATERIAL.

The material on which this investigation is based was obtained during the last half of the year 1915 and the first two months of 1916, when the writer was pathologist to No. 21 General Hospital. This unit arrived at the end of May, 1915, and began taking in cases about the middle of June. The cases admitted were nearly all from the Gallipoli peninsula or from Mudros. At first the cases were mainly surgical, but as the campaign in Gallipoli progressed the medical cases increased in number until, at the end of the year, the cases were almost entirely medical.

The chief epidemic diseases were enteric and dysentery. During the last six months of 1915 the admissions on the medical side were 5,300 in number. 1,723 were classed as enteric; of these 98 died, giving a mortality of 5·688 per cent. 1,146 cases were classed as dysentery. (This number does not include patients admitted for wounds, &c., who were suffering from mild dysentery or who developed clinical dysentery subsequent to their admission. Nearly everybody on the peninsula suffered from diarrhoea, and cases were not classed as dysentery unless there was tenesmus, and blood and mucus were passed, or unless pathogenic amoebae or dysentery bacilli were found in the faeces.) Fifty-six patients died from dysentery, giving a mortality of 4·886 per cent. (This number does not include patients who died from wounds, &c., and were found to have dysenteric ulcers in the post-mortem room.) Thus more than half the medical cases during this period were classified as enteric or dysentery. For these figures I am indebted to Major Kerr, officer in charge of the medical division.

It will be seen from my summaries of faecal examinations and post-mortems that the epidemic of dysentery was severe from August to December, 1915. The epidemic was present before August and after December, but it was during these months that the epidemic was severe. The ' bloody flux ' then sent a great number of men from the peninsula.

PART II. HISTORY AND ACKNOWLEDGEMENTS.

On arriving I visited the hospitals already established. At No. 15 General Hospital, Capt. Haig, officer in charge of the pathological laboratory, gave me many useful items of information on the diseases with which he was dealing. He had had (middle of June, 1915) sporadic cases of amoebic dysentery and showed me one typical colon. At No. 17 General Hospital, Capt. R. G. Archibald (formerly pathologist to the Wellcome Research Laboratory at Khartoum) was in charge of the pathological laboratory, with Lieut. Willmore as his assistant. Here also there was amoebiasis. Capt.

Archibald later proceeded to Mudros as officer in charge of the Central Laboratory, and his valuable observations reached us in Alexandria from time to time. Thus in the middle of June there were definite indications of the probability of an epidemic of dysentery.

My own laboratory equipment was at first very inadequate; local stores and laboratories however yielded some material, and Professor Wilson, of the Cairo Medical School, most kindly brought down some urgently needed equipment from his own laboratory. He also gave me invaluable voluntary assistance in the work, so that we were soon able to do some of the more simple investigations so urgently needed for the diagnosis of the cases.

My thanks are also due to Lieut.-Col. Robinson, C.M.G., officer in charge of the hospital. His knowledge and experience of the diagnosis and treatment of dysentery enabled us to diagnose and treat dysenteric cases efficiently with emetine from the commencement of the epidemic.

Towards the end of July the Hunter Sanitary Commission and Lieut.-Col. Sir R. Ross arrived and visited the hospitals. At the time of the Commission's first visit to No. 21 General Hospital there had been three postmortems on cases of amoebic ulceration of the colon, and about thirty cases had been diagnosed by finding pathogenic entamoebae in the stools. Similar, but more extensive, findings had, I believe, been made by Capt. Archibald at No. 17 General Hospital. Thus at the end of July we were fully alive to the likelihood of a severe epidemic of amoebic dysentery.

Lieut.-Col. Sir R. Ross settled down at No. 21 General Hospital and investigated dysenteric cases. To Sir R. Ross I am indebted for much kindly encouragement and assistance in my work. In my opinion, and in that of nearly all the workers in Egypt, his action in advising emetine to be given *early* in *all* cases of dysentery (middle of August, 1915) saved the forces from a greatly increased mortality. The benefit of the early administration of emetine was immediately shown by the improved condition on admission of cases which had been so treated on the peninsula or hospital ships. Cases could not reach the hospital till four or five days after they had reported sick on the peninsula. The majority of the cases took longer than this to reach hospital.

On the advice of the Hunter Commission a central laboratory was formed. They fixed their quarters at No. 21 General Hospital, with Major A. R. Ferguson, Professor of Pathology to the School of Medicine, Cairo, in charge. Thus, in the later stages of the epidemic, I had the advantage of investigating cases in conjunction with the staff of this laboratory.

Capt. John G. Thomson, M.B., formerly Lecturer on Protozoology to the London School of Tropical Medicine, paid short visits to my laboratory and, after a period as officer in charge of a convalescent typhoid camp, returned to Alexandria as protozoologist to the Central Laboratory. He gave me much instruction in regard to the identification of the protozoa in the faeces. His cheery personality, combined with immense skill and enthusiasm for his work,

will always be remembered by those who were fortunate enough to work
with him.

I have acknowledged in my reports of cases the work of Capt. A. Davies,
M.D., formerly pathologist to the Seamen's Hospital, Greenwich, and of Lieut.
W. Magner, M.B., formerly Demonstrator of Pathology and Bacteriology to Uni-
versity College, Cork, who were also on the staff of the Central Laboratory.
The reports of this and other central laboratories were circulated privately. It
is to be hoped that they will be collected and published, because these observa-
tions at first hand of the acute cases in the epidemics are obviously of more
value than observations made in England on convalescent cases. Some of the
observations made in England have been published (1915 and 1916), and, as was
to be expected, most of them give an erroneous impression of the aetiological
factors in the epidemics on the Gallipoli peninsula.

On October 15, 1915, there was a discussion on the treatment of acute
dysentery under the presidency of the principal Director of Medical Services.
This discussion revealed a universal belief in the benefits derived from emetine
treatment; it was printed and deserves a wide circulation.

On October 31, 1915, at a meeting of pathologists held in Alexandria,
I brought forward the view, based on thirty-three post-mortems and the examina-
tion of about 700 specimens of faeces for protozoa, that we were dealing with
an epidemic of amoebic dysentery and that this amoebic dysentery was fre-
quently complicated by other infections; for instance, typhoid and paratyphoid.
I had obtained no satisfactory evidence of a primary specific bacillary dysentery.
This view was almost universally supported by the observations of other
pathologists, notably by Capt. Archibald, who, working at Mudros, got his cases
on the average at an earlier stage of the disease. He gave us the interesting item
of information that the Turkish prisoners were frequently found to be suffering
from amoebic dysentery. Professor Kartulis confirmed the great preponderance
of proved amoebic cases. On the other hand, Lieut. Willmore, the well-known
expert on bacillary dysentery, considered that the epidemic was then becoming
bacillary. The results of my investigation set forth in this paper do not support
this view, except in so far as they show that amoebic dysentery may be com-
plicated by bacterial infection.

In the latter part of February, 1916, I proceeded to establish a laboratory
at No. 27 General Hospital. There we dealt mainly with convalescent cases
from the homes and hospitals which were being evacuated. Amongst these
convalescents many carriers of tetragena cysts were found. The observations
made in this hospital are not included in this report, which deals solely with
the acute cases in the epidemic. The systematic investigation of a large number
of faeces for cyst carriers was being undertaken by Lieut.-Col. Wenyon, who had
recently come out.

On returning to England in April, 1916, I applied for leave to investigate
the dysenteric material which I had brought or sent back from Egypt. The
War Office authorities referred me to the Medical Research Committee. I there-

fore resigned my commission and was given a research grant by the Medical Research Committee.

I am indebted to Dr. H. M. Turnbull, Director of the London Hospital Pathological Institute, for permission to occupy my old quarters and utilize the resources of the laboratory. Dr. Turnbull has given me much valuable advice and assistance in the histological work and preparation of this paper.

I should like to record my grateful thanks to the Clinical Staff at No. 21 General Hospital; throughout the epidemic they assisted me with clinical observations and were not too exacting in their demands on the pathologist. I sincerely hope that some of them may find time to record their clinical observations. Throughout the work I was ably assisted in the laboratory by Corpl. Holden. I regret to say that in the course of his duties he developed a slight attack of amoebic dysentery, and being apparently cured after a course of four grains of emetine, returned to work. Some months later, after I had returned from Egypt, he developed a severe attack and was invalided home. He was thus an example of the dangers of too short a course of emetine treatment. I certainly could not have got through half the essential work had I not been able to leave the making of media, &c., in the hands of so reliable an assistant.

I wish to record my thanks to Mr. W. T. Shiells and Mr. J. R. Ford for the care with which they have pictured the macroscopical and microscopical specimens which illustrate this paper.

PART III. METHODS OF EXAMINATION EMPLOYED AND RECOMMENDED.

Section 1. Examination of Faeces for Protozoa.

(a) *Method of examining unstained faecal films.* The faeces were obtained as fresh as possible; the bed-pans were brought direct to the laboratory; it was found advantageous to have the whole specimen to examine with the naked eye. Instructions were issued to avoid, as far as possible, contamination of faeces with urine, paper, and disinfectants. Suitable portions of the specimen were selected and placed in test-tubes; the bed-pans were then taken away by the orderly.

A microscopic examination of unstained portions of the specimen was first made. A small portion, preferably containing blood and mucus, was removed with a platinum loop, and placed on a slide; a coverslip was then pressed down fairly firmly. The film was examined under a $\frac{1}{6}$ lens (Spencer) with a No. 4 (Spencer) eyepiece. The condenser was turned well down and the diaphragm closed until the desired refraction was obtained.

Entamoebae and cells may be identified with a $\frac{2}{3}$ or 1″ lens and the finding confirmed by a higher power; this procedure, however, does not save time. A $\frac{1}{12}$″ oil immersion was seldom used. A warm stage was not necessary in Egypt.

It was found best to avoid diluting the faecal material with saline; the diluting fluid may contain foreign bodies or even protozoa. In some richly cellular or solid specimens dilution with saline may be necessary, but in most

cases a little practice in selecting specimens and diluting with faecal fluids enables one to make a film of a density convenient for easy examination. The addition of either a drop of iodine solution, to render nuclei conspicuous, or of a dilute solution (1 in 10,000 of normal saline) of neutral red, to differentiate the cytoplasm of amoebae from that of other cells, was found to be of no practical advantage. Stained films were found to be an essential supplement to the examination of fresh unstained material.

(b) *Method of making and staining wet-fixed faecal films.* The following directions describe the methods which were found by experience to be best :

1. Make, on a slide or coverslip, a film from the fresh stool, choosing either a mucous or a fluid portion according to the result of unstained film examination. The film should be thin and made rapidly with a platinum loop. If considered advisable, the actual film which has been examined unstained may be utilized, the coverslip being drawn off gently. Place the film gently *while wet* in filtered Zenker's fluid.

Zenker's fluid (modified) :
    Bichromate of potassium . . . . . 2·5 grm.
    Corrosive sublimate . . . . . 5 grm.
    Water to . . . . 100 c.c.
Add immediately before use—
    Glacial acetic acid . . . . . . 5 c.c.

Leave to fix for 5–10 minutes.

Films occasionally tend to wash off. This may be avoided by gentle manipulation. In some cases it was found advisable to add a little blood to the mucus. The blood plasma helps the mucus to fix on the slide, and also improves the staining of the specimen. For this device I am indebted to Capt. D. Thomson. Occasionally it may be necessary to let the outer portion of the film partially dry ; the central portion will then be fixed wet. It is essential that the portion to be examined should be fixed while wet. The slide should never be allowed to dry during the rest of the fixing and staining processes.

2. Transfer the film directly to absolute alcohol and leave for 5–10 minutes, not longer.

3. Transfer direct to 80 per cent. alcohol.

Films will keep for some hours or days in this, but it is best to leave for a short time only, 10–20 minutes, changing the solution twice. If the fixative is filtered before use there should be no deposit on the film. If mercuric oxide is deposited, the film may be treated with Lugol's iodine solution.

Proceed to stain the film with Weigert's iron-haematoxylin and van Gieson's stain (for prescriptions see later under staining of sections), i. e. :

4. Stain with Weigert's iron-haematoxylin : 5–10 minutes.

5. Wash in tap-water till black : 10–20 minutes.

6. Differentiate in acid alcohol : 30 seconds or more.

This should be done thoroughly ; the haematoxylin will remain firm in the nuclei.

7. Wash in tap-water till slate grey in colour : 10–20 minutes.

8. Stain with van Gieson's stain : 1 minute 30 seconds.

9. Dip in tap-water to differentiate the van Gieson's stain ; then flush the film immediately with absolute alcohol. This differentiation should be rapid ; if washed too long in water all the yellow picric stain is removed and red fuchsin only is left.

10. Dehydrate in absolute alcohol.

11. Clear with xylol.

12. Mount in Canada balsam.

The nuclear chromatin of amoebae and body cells is stained black ; the characteristic nuclear structure of the amoebae is conspicuous.

The cytoplasm of the vegetative entamoebae retains much of the haematoxylin stain, but it can be decolorized almost entirely without decolorizing the nucleus.   The cytoplasm of body cells is stained various shades of yellow.

Red blood corpuscles are bright yellow.

This method is much more rapid than that of Heidenhain's iron-haematoxylin, which is commonly used for amoebae.   Differentiation by acid alcohol is rapid and complete.   The use of the counterstain is also an advantage.

A large number of films can be dealt with at the same time, and the staining technique can be carried out by any intelligent laboratory assistant.

The following fixative for wet films was found to give results quite as good as Zenker's fluid.   I think that it was suggested by Capt. J. Thomson.

1. Modified Schaudinn's fluid, i.e.:

Normal saline saturated with corrosive sublimate   .   60 c.c.
Absolute alcohol (commercial)   .   .   .   .   .   30 c.c.
Glacial acetic acid, added just before use .   . 2·5 or 5 c.c.

Fix for 5–10 minutes.

2. Transfer direct to 70 per cent. alcohol and leave for 1 hour or more.

3. Stain by Heidenhain's iron-haematoxylin or any other stain.

The following methods of staining wet-fixed faecal films have been found useful in the study of the differential cytology and protozoology :

Twort's light green and neutral red; this is in some degree differential for the vegetative entamoebae.

Mucicarmine stain for mucous epithelial cells.

Jenner's stain for neutrophil, eosinophil, and basophil leucocytes.

Unna Pappenheim's stain for plasma cells.

Giemsa's stain.

Carbol thionin blue.

Section 2.   Post-mortem Examination.

The majority of the post-mortems were performed within twelve hours of death.   If done more than twelve hours after death the post-mortem changes tended to be severe, but even during the hot summer weather decomposition was not so rapid as to preclude post-mortem examinations except in occasional obese or extremely septic subjects.   I have demonstrated intact amoebae in sections obtained from a post-mortem performed more than twelve hours after death.

Post-mortems were performed in the thorough routine manner of the London Hospital Pathological Institute.   The head was not invariably examined ; this is to be regretted, but there were other urgent calls on the time of the pathologist. I would emphasize that in dysenteric investigation an incomplete post-mortem may be just as deceptive as an incomplete examination of faeces.

(*a*) *Special points* to note in performing post-mortems on dysenteric cases are :

1. The condition of the *veins in the subserosa* and mesentery of the colon. A marked dilatation of these veins is characteristic of all forms of dysenteric ulceration of the colon.   Films of blood from these veins should be examined for amoebae, &c.   Larger veins should be opened up and clots removed for examination.

Vegetative entamoebae and other abnormal cells were found in the dilated subserous veins; it is thus possible to compare the cytology of the blood stream with that of the faeces in amoebic dysentery.

2. *The intestines* should be separated from the mesentery and removed complete from the duodeno-jejunal flexure to the anus.   They should be opened

with care and washed by shaking gently in a bucket of water. The site and
extent of lesions may conveniently be noted in diagrammatic form (see diagrams
in Leonard Rogers' book on the Dysenteries).

As stated below in the description of the morbid anatomy of dysentery the
appearance of the lesions caused by amoebiasis in the colon in different cases and
in individual cases varies greatly. The prevailing lesions in some cases have the
typical text-book appearance of acute and subacute amoebic dysentery, in others
the appearance of sporadic ulcerative colitis, and yet in others an appearance
resembling that of acute bacillary dysentery. Further, amoebae are more likely
to be found in certain lesions than in others. In order, therefore, to ensure that
amoebic infection is not overlooked, a thorough search should be made for the
lesions most valuable in diagnosis. Minute lesions are of great value for
diagnosis by films of scrapings or by microscopic sections. Raised nodules,
having a diameter from that of a pin-head to that of a pea and showing a yellow
necrotic centre, should especially be searched for. Well-defined round or oval
ulcers with a raised undermined edge and containing lemon yellow gelatinous
débris are also important.

Lesions of the above two types are almost diagnostic of amoebic dysentery.
Such nodules and small ulcers containing gelatinous yellow débris almost
invariably contain entamoebae. By a careful examination of scrapings from
beneath the edge of the ulcers, examined both unstained and stained (see pp. 189,
190), an accurate diagnosis may frequently be made. In intestines having the
appearance of acute bacillary dysentery all the amoebic lesions may be obscured
by a green diphtheroid membrane on the surface of the ulcer and mucosa. In
such cases suspicious areas should be incised, and portions should be taken for
microscopic sections from any areas in which ulceration involving the submucosa
is revealed.

For the demonstration of amoebae in tissues it is extremely important that
a number of the small lesions should be preserved for sections. In places where
ulceration is advanced or where necrosis and secondary inflammation are severe,
it may be impossible to demonstrate entamoebae in the tissues. Such lesions
are end products of the processes of amoebic ulceration ; and if they alone are
examined a wrong diagnosis may be made.

Before making a diagnosis on post-mortem material it is important that the
pathologist should know the treatment which has been adopted during life.
After a thorough course of emetine treatment typical undermined ulcers may fail
to show entamoebae. The treatment may, however, fail to eliminate amoebae ;
it is important, therefore, that the smaller lesions should be examined in all
cases by films of scrapings and by microscopic sections.

The small intestine may show inflammatory changes in its lower part. If
it does, care should be taken to exclude enterica infections, because the para-
typhoids may show rather atypical enteric lesions.

3. *The colic lymphatic glands* should be carefully examined. They seldom
show severe inflammatory changes in uncomplicated dysentery. If there is
marked inflammatory change, care should be taken to exclude enteric or other
septicaemias by bacteriological examination of glands, gall-bladder, and spleen.
In all cases glands should be preserved for section.

4. *The liver* should be removed complete and sliced evenly. A careful search
should be made for small abscesses or minute necroses. Portions of liver, however
normal in appearance, should be preserved for sections ; they may show portal
infiltration or hepatitis. Portal and hepatic veins should be opened up and
clots removed for examination, not only in cases of liver abscess, but also in
other cases.

5. *The kidney* should be examined carefully, and portions be preserved for
sections.

6. *The spleen* should be weighed. If septic, an attempt may be made to

identify pathogenic organisms by culture.   Portions should be preserved for sections.

7. *The urinary bladder* should be opened carefully in front, and examined for lesions about the trigone.

8. *The suprarenals* should be examined for haemorrhages.

9. *The heart* seldom shows changes; portions should be preserved for the demonstration in sections of minor degrees of fatty degeneration.

10. *The lungs* should be examined for haemorrhagic and necrotic foci.

11. *The brain* should be examined.   Amoebic abscess has been described.

(*b*) *Preservation of material for sections.*   Suitable portions of the intestine, including the smaller lesions in the colon, and portions of other organs should be removed at post-mortem and placed in 4 per cent. saline formaldehyde, i. e.

> Commercial formalin (40 per cent. formaldehyde)   .   10 c.c.
> 0·9 per cent. saline solution   .   .   .   .   .   90 c.c.

This fixative was found to be more satisfactory for general purposes than Zenker's fluid.   It preserves amoebae excellently.   The portions of tissue should be trimmed and placed in fresh 4 per cent. saline formaldehyde the next day. Material may be left indefinitely in this solution.   My own material was forwarded to England in this solution in small glass bottles, the corks of which had been sealed with paraffin.   The sections obtained after arrival were quite satisfactory; in most of the sections the amoebae showed excellent nuclear detail and cytoplasmic structure.

(*c*) *The preservation of macroscopic specimens.*   In many cases it is advisable to preserve the intestine or other organs intact, either as museum specimens or for further investigation.

In making any morbid anatomical investigation it is important to have the whole specimen at disposal for purposes of reference.   The first description of the lesions can seldom be full enough to be entirely satisfactory.   Therefore it is advisable, whenever possible, to preserve the whole specimen.

The intestine should be pinned out flat, but not stretched tightly, mucous membrane uppermost, on a board, and placed in the following modified Kaiserling's No. 1 solution:

> Commercial formalin   .   .   .   .   .   .   800 c.c.
> Water .   .   .   . 4,000 c.c.
> Potassium acetate (crude)   .   .   .   .   .   85 grm.
> Potassium nitrate (crude)   .   .   .   .   .   45 grm.
> Glycerin   .   .   .   .   150 c.c.

After a day or two the specimen should be placed in fresh clean solution. If necessary, portions of tissue, preserved in this solution, may be taken for section at a later date.   The fixative has no harmful action on the tissues, though penetration, when tissues are fixed in bulk, is slow.

Many of my specimens, after preservation in this manner, were wrapped in lint which had been soaked thoroughly in the solution, were then packed in a tin-lined 'reserve dressing' box, soldered down and sent home to England. Although packed in this manner for more than three weeks they were moist on arrival, and, when put through other solutions, made satisfactory museum specimens.   Material for sections taken from these specimens gave satisfactory results.

Section 3.   *Demonstration of Amoebae in Sections of Tissues.*

In selecting portions of material preserved in 4 per cent. saline formalde-
hyde or Kaiserling's solution for microscopical sections it was found best, when
possible, to include a large area of intact mucosa on either side of the lesion and
a portion of the mesentery.   The selected portions were embedded in paraffin in
the ordinary way.   It was found best to cut large sections ; for these a sliding
microtome is necessary.

The staining methods found most useful for demonstrating amoebae in the
tissues were :

Ehrlich's acid haematoxylin counterstained by eosin.

Weigert's iron haematoxylin counterstained by van Gieson.

Twort's mixture of light green and neutral red.

Many other methods were tried, e. g. Heidenhain's iron-haematoxylin,
Jenner's stain, Unna Pappenheim's stain, carbol thionin blue, &c. ; but the
above three methods were found most satisfactory.

Weigert's iron-haematoxylin counterstained by van Gieson's mixture brings
out the detailed structure of the amoebae.   Twort's stain demonstrates their
presence in tissues under a low power.   These stains may, moreover, be used for
wet-fixed faecal films, and thus, if permanent preparations of faeces from the
living patient are made, they may be compared with the cytological appearances
seen in sections from material obtained after death.

(*a*) *Prescriptions and technique for staining sections by Weigert's iron-
haematoxylin and van Gieson.*

1. Remove paraffin with xylol.
2. Remove xylol with alcohol.
3. Stain with Weigert's iron-haematoxylin.

Stock solution A. 1 grm. of haematoxylin in 100 c.c. of 96 per cent. alcohol.

Stock solution B. Liquor ferri perchlor. fort. (B. P.) .   .   2 c.c.
                   Distilled water   .   .   .   .   .   97 c.c.
                   Hydrochloric acid .   .   .   .   .   1 c.c.

Mix equal quantities of A and B just before using.
Stain for 10 minutes.
4. Wash in tap-water till black : say 20 minutes.
5. Differentiate thoroughly in acid alcohol, i. e.

      70 per cent. alcohol .   .   .   .   .   .   100 c.c.
      Hydrochloric acid   .   .   .   .   .   .   1 c.c.

This takes 1–2 minutes; it is difficult to overdo it ; haematoxylin will
remain firm in the nuclei.
6. Wash in tap-water till a delicate grey blue colour : say 20 minutes.
7. Stain in van Gieson's stain, i. e.

      1 per cent. watery solution of acid fuchsin   .   .   5 c.c.
      Saturated solution of picric acid   .   .   .   100 c.c.

Mix and keep in stock bottle.
Stain for 1½ minutes.
8. Dip rapidly in tap-water to differentiate the van Gieson's stain.
9. Dehydrate immediately with absolute alcohol.
10. Clear with xylol.
11. Mount in Canada balsam.

In order to prevent fading of the picric stain, it is advisable to add a few
crystals of picric acid to the balsam.

Nuclear detail of tissue cells is sharp, the chromatin being stained black.

The vacuolated cytoplasmic reticulum of the vegetative entamoebae has an affinity for the haematoxylin, but a thorough differentiation with acid alcohol will remove most of the haematoxylin from the cytoplasm, leaving the nucleus brightly stained; the characteristic structure of the nucleus is demonstrated.

The cytoplasm of all tissue cells is stained various shades of yellow.

Red blood corpuscles are bright yellow.

Collagenous fibres are bright red.

Elastic fibres are bright yellow.

Fibrin is yellow.

(*b*) *Prescriptions and technique for staining sections by Twort's light green and neutral red stain.*

1. Remove paraffin with xylol.
2. Remove xylol with absolute alcohol.
3. Remove alcohol with distilled water.
4. Stain for 2–5 minutes in

Glycerin alcohol stain solution . .   .   .   . 2 parts
Distilled water.   .   .   .   .   .   . 1 part

The stain solution can be obtained from Baird and Tatlock. The technique of its manufacture is too complicated to give here. It is best to mix the stain and distilled water in a graduated measure immediately before use. In order to avoid a deposit of granular precipitate from the stain it is best to invert the slide on the staining solution.

5. Rinse in distilled water.
6. Fix in a solution of Unna's glycerin ether mixture (2 per cent. in distilled water) for $\frac{1}{2}$–1 minute.

If the red stain is seen to flow out, the slide must be removed instantly.

7. Rinse in distilled water.
8. Blot the slide. Differentiate and dehydrate in equal parts of absolute alcohol and xylol. The red stain comes out rapidly.
9. Clear with xylol.
10. Mount in Canada balsam.

Nuclear chromatin of tissue cells is stained bright red. The cytoplasm of tissue cells is stained various shades of green. Mast cells show bright red granules in their cytoplasm, and nerve ganglion cells show some red granules.

In vegetative entamoebae the vacuolated cytoplasmic reticulum is stained bright red. This renders the amoebae very obvious under a low power.

Red blood corpuscles are bright green.

Tissue fibrils and necrotic débris are bright green.

Entamoebae in the débris of a liver abscess thus show clearly against the green background of necrotic débris.

Fibrin is green. Bacteria are bright red.

I have found this stain very useful for demonstrating the presence of entamoebae in sections of tissues; it is in some degree differential for entamoebae, though it is not a good stain for demonstrating their minute structure and nucleus. An iron-haematoxylin stain is essential for this purpose.

Some practice is needed in order to obtain satisfactory results; the test of efficiency is a clear bright red staining of nuclei of tissue cells and a green staining of their cytoplasm.

Section 4. Other Lines of Investigation.

I have given very fully the methods employed for a cytological investigation of the faeces and for the investigation of morbid anatomy. I have given them thus fully because I hold that these simple, well-proved methods of

investigation have been, and are being, neglected. I do not wish to magnify their importance, but I do most emphatically maintain that in investigating dysenteries these fundamental procedures cannot be neglected.

For a satisfactory study of dysentery it is imperative that investigation should proceed on all possible lines *simultaneously*. I greatly regret, therefore, that the lines of investigation tabulated below were not carried out more systematically. In the later stages of the epidemic Lieut. W. Magner, of the Central Laboratory, devoted his entire attention to the bacteriology and serology of the disease. His results published in the *Lancet* of October 21, 1916, are very significant and indicate the advisability of a more extensive investigation along these lines.

1. Examination, ante and post mortem, of faeces for dysenteric and enteric bacilli.

2. Examination, ante mortem, of blood for bacteria.

3. Examination, ante and post mortem, of blood serum for specific agglutinins.

4. Examination, ante mortem, of blood for cytological changes.

Such results of faecal and blood culture as were obtained by myself and the workers at the Central Laboratory were at first somewhat confusing, but when the frequent association of amoebic dysentery with enterica infections and other septicaemias of intestinal origin was recognized in the post-mortem room many of our results were explained.

I would suggest that systematic blood culture in acute cases would throw more light on the pathology of dysentery than the culture of faeces. A great variety of organisms was found in the blood stream in the cases of severe amoebic ulceration of the colon, and it was obvious that amoebic dysentery was frequently complicated by bacteraemia. I would emphasize especially the importance of blood culture in cases with sustained pyrexia, because pyrexia in amoebic dysentery suggests a mixed infection. It was indeed occasionally found possible to diagnose amoebic dysentery plus enterica infection and amoebic dysentery plus bacillus coli infection by a study of the temperature chart.

The agglutination results were for the same reasons equally confusing. An indication of the variety of bacterial infection which may complicate amoebic dysentery may be found in the results of the agglutination tests published by Captains Arkwright and York, with Lieutenants Priestley and Gilmore, in the *Royal Army Medical Corps Journal* for December, 1916.

The examination of blood for cytological changes was undertaken by Professor Wilson. A marked leucocytosis was noted in most of the cases of proved amoebiasis. From the examination of faeces and post-mortem material it appeared that the higher the count the more severe the ulceration and the worse the prognosis. Cases, however, with very high counts, e.g. 34,000 per c.mm., recovered. I came to the conclusion that the leucocytosis depended on the intensity of secondary bacterial infection and haemorrhage. It is to be hoped that Professor Wilson will find time to publish his results.

PART IV. RESULTS OF EXAMINATION OF STOOLS.

Section 1. *Differential Characters of Contents of Stools.*

Before analysing the results of the routine examination of the various stools sent for diagnosis, it is convenient to describe the differential characters of certain of the cells and organisms found therein.

(a) *Vegetative entamoebae histolytica or tetragena*, i. e. the pathogenic entamoeba (see Figs. 1–9, Plate 26).

In unstained films this organism varies from the size of a neutrophil leucocyte to a size larger than the largest phagocytic endothelial cell. It is conspicuous because it is refractile and has a pale blue or green colour. The colour in Egypt was bluish, whilst in England, with its dull skies, it is greenish. It shows a thin outer margin of clear ectoplasm. The rest of the body, the endoplasm, is finely reticular and frequently vacuolated. The vacuoles vary greatly in size, are generally numerous, and may show a faint pink colour; they are not contractile. The endoplasm may contain red corpuscles either of normal size or shrunken. The endoplasm may also contain solid rounded lumps of chromatin. I have never been able to satisfy myself that these lumps of chromatin are the remains of ingested leucocytes, lymphocytes, or other body cells. Generally the typical nucleus may be identified as a small sharply defined ring with the chromatin evenly distributed or forming crescentic thickenings on the nuclear membrane. The nucleus is generally excentric. Entamoebae, when stationary, are generally rounded, and the rounded form is far commoner than the active form. When moving actively the entamoeba is very easily identified. It pushes out finger-shaped or broad blunt pseudopodia consisting of clear highly refractile ectoplasm; the spongy or vacuolated endoplasm with contained bodies and nucleus flows to accommodate itself to the altered shape. Movements of the endoplasm are frequently obvious when the ectoplasm shows no movement. Occasionally the nucleus may be seen to change its shape in response to alterations in its environment. The amoeba rapidly changes its form and advances past obstructions by accommodating its shape to the spaces between obstructions. It generally appears to progress in a casual manner, changing its direction for no obvious cause. When very active it may be seen to engulf red blood corpuscles. This phenomenon was very seldom observed by me, although entamoebae containing a large number of red cells were frequently seen. The only points of differential diagnosis between the vegetative pathogenic entamoeba and the ' non-pathogenic ' entamoeba coli which I can give are :

Pathogenic Entamoeba.	*' Non-pathogenic' Entamoeba.*
1. Glassy refractility and green or blue tint.	Much less refractile and of greyish tint.
2. Frequently contains many red cells.	Seldom, ? never, contains any red cells.
3. Amoeboid movements sometimes very rapid.	Amoeboid movement never rapid.
4. Nucleus not very obvious and generally shows little chromatin.	Nucleus obvious and contains much chromatin.
5. Clear differentiation between ecto- and endoplasm.	Ectoplasm difficult to differentiate from endoplasm.

It will be seen that these criteria do not suffice to give a certain differentiation in all cases between pathogenic and ' non-pathogenic ' entamoebae.   If the entamoebae are very active or contain many red cells, or show a distinct differentiation of ecto- and endoplasm, they are certainly pathogenic entamoebae. Pathogenic vegetative entamoebae may, however, show none of these characteristics.   Thus, in scrapings which I made from intestinal ulcers at the post-mortem examination of one patient who died from liver abscess, the amoebae, though highly refractile, did not contain red cells ; moreover, their movements were sluggish and their nuclei were very obvious.   I am, therefore, not at present satisfied that any of the criteria given as yet by protozoologists are sufficient to enable a differentiation to be made with certainty in all cases between pathogenic and ' non-pathogenic ' vegetative entamoebae.   That is, I consider that in the present state of knowledge it is impossible with certainty to say that a vegetative entamoeba in a dysenteric stool is non-pathogenic.   It follows, therefore, that in practice it is the safest plan to consider all vegetative entamoebae occurring in dysenteric stools as pathogenic, and to treat the cases accordingly.

In stained films and also in sections vegetative entamoebae show similarly a great variation in size.   Their staining reactions are very typical and serve to differentiate them readily from the cells of the human body.   *With Weigert's iron-haematoxylin and van Gieson's stain* the whole amoeba is markedly haematoxyphil ; the vacuolated cytoplasmic reticulum retains the haematoxylin stain to a far greater degree than any human body cell.   Contained red corpuscles are yellow in colour.   The nucleus typically is a small sharply defined ring. The scanty chromatin being confined to the rim with the occasional exception of a nodule of chromatin in the centre of the nucleus, the nucleus does not show any network of chromatin.   There are frequently, however, variations from this appearance of the nucleus ; the figures (Plates 26 and 29) given of amoebae in tissues and films are more eloquent than pages of description.   One notable variation is condensation of chromatin in one or more fusiform or crescentic thickenings on the margin of the nucleus.   Such appearances of the nucleus are said to be degenerative, but entamoebae showing them are certainly actively motile. *With Twort's light green and neutral red stain* the whole vegetative entamoeba takes the red stain ; its cytoplasmic reticulum is stained as brightly as the nuclei of the neighbouring tissue cells, but the cytoplasm of these tissue cells is stained green.   Mast cells, however, have bright red granules in their proto-plasm, and nerve ganglion cells also show some red granules.   Red blood cells contained within the amoeba are stained green.   The nucleus of the amoeba can be recognized, but is not clearly differentiated from the cytoplasm by this stain.   *With Jenner's stain* the cytoplasm of the amoeba is bright blue and vacuolated.   *With Unna Pappenheim's stain for plasma cells* the whole amoeba is brightly stained bluish green and is vacuolated.

   (b) ' *Refractile cells.*'   (See Figs. 11–18, Plate 27.)   Under this heading I include a well-defined group of rounded or oval cells which have been described by various observers as vegetative entamoebae, stages in cyst formation, dividing

forms, &c.   They are almost invariably present in faeces along with vegetative entamoebae, and also commonly occur in dysenteric faeces when vegetative entamoebae are absent.   They are usually numerous.   *In unstained films* they are seen as extremely well-defined rounded cells, which are more refractile than the human body cells, but less refractile than the vegetative entamoebae ; they are greyish rather than greenish in colour.   They vary in size from that of a neutrophil leucocyte to a large phagocytic endothelial cell.   Their nuclei are very conspicuous and fully as refractile as the cytoplasm of a vegetative entamoeba.   The nuclei may be single and of small size, or may be multiple.   When multiple they may be two, four, or more in number, and may be of equal or unequal size.   The nuclei show characteristic crescentic thickenings on their margins.   In some cells these curious nuclei are large, almost filling the cell ; such large nuclei occasionally contain motile granules.

In stained films these cells are very obvious.   Their cytoplasm is finely spongy and occasionally vacuolated.   The cytoplasm is more haematoxyphil than that of the body cells, but less haematoxyphil than the cytoplasm of the vegetative entamoeba.   With Twort's stain the cytoplasm is green, and thus differs from that of the vegetative entamoeba.   The nuclei are characteristic ; they show well-defined crescentic thickenings on their margins.   The following nuclear forms are so frequent that they may be noted :

> Single excentric nucleus ;
> Double excentric nucleus ;
> One large and one small nucleus ;
> Two large and two or more small nuclei ;
> Large nucleus nearly filling cell.

I would emphasize that in examining stained films I neglect all cells with fragmented nuclei.   I have figured (Plate 27) a number of refractile cells, for I consider them characteristic of dysenteric faeces.   The differential diagnosis of these cells was worked out as follows :

1. I failed to find them in other inflammatory secretions, e. g. muco-pus from nose, &c.

2. They were not degenerate epithelial cells.   They were rounded, never columnar.   Their protoplasm as a rule was not degenerate ; it never contained mucus (mucicarmine stain).   The nuclei were too frequently multiple.

3. They were not altered neutrophil, eosinophil, or basophil leucocytes.   The majority of the cells were too large.   The protoplasm never contained characteristic granules in Jenner's stain, &c.

4. They were not altered plasma cells, for their protoplasm was never stained characteristically by Unna Pappenheim's stain.   Multinucleated plasma cells are not infrequent in sections of the gut in amoebic dysentery, and at first I tried to class the refractile cells as plasma cells with degenerating nuclei.   When compared with ordinary plasma cells in faeces and sections I found this view was not tenable.   The refractile cells were as a rule far too large, and their nuclei never corresponded to the clock-face type of the plasma cell nucleus.

5. They were not altered lymphocytes. The majority were much too large. Their cytoplasm was relatively far too abundant. Nuclei having the structure of the lymphocytic nucleus were never present.

6. They bore no resemblance to squamous epithelial cells.

7. They were not ordinary endothelial cells, for their nuclei as a rule were much too small. Phagocytic endothelial cells, macrophages, are numerous in dysenteric faeces and in sections of dysenteric lesions. For a considerable time I endeavoured to look upon these refractile cells as macrophages. It appeared to me possible that the refractile cells might be phagocytic endothelial cells in which the true nucleus had undergone chromatolysis or karyorrhexis, whilst the nuclei of the engulfed cells remained, after undergoing a curious form of degeneration. Phagocytic endothelial cells certainly lose their true nucleus frequently. I have, however, studied macrophages in the sinuses of lymph glands and in other inflammatory foci and have failed to find nuclei similar to those in the refractile cells. It is necessary to add that in stained films there are a number of rounded cells, containing fragments of chromatin, which I cannot identify; many of these appear to be degenerate 'refractile cells', others may be degenerate phagocytes or even degenerate amoebae. For the purposes of this paper I have excluded such cells from consideration.

The rest of the cells constantly found in dysenteric faeces are ordinary tissue cells or inflammatory cells. In appropriately stained films they can be recognized by any cytologist and cannot be confused with the vegetative entamoeba.

(c) *Endothelial cells.* (See Figs. 19–24, Plate 28.) *In unstained films* clumps of large polygonal or rounded cells and isolated rounded cells are frequently seen. These cells are not refractile. They have a large nucleus which shows a definite reticular structure. Some of the isolated cells are very large and have an excentric nucleus. They may contain leucocytes, lymphocytes, or red blood cells. The contained cells lie generally within a large vacuole. Some of these phagocytic cells are fully as large as the larger vegetative entamoebae and it may be difficult to differentiate them from amoebae in the unstained film.

In stained films the clumps of large endothelial cells are easily recognized. From a study of sections I conclude that these came from blood-vessels. The large phagocytic endothelial cells are similar to those seen in the sinuses of an inflamed lymph gland. If the large reticular nucleus is present the cell is easily identified. This nucleus, however, is frequently degenerated whilst the nuclei of contained lymphocytes or leucocytes are intact. In this way curious effects are obtained. I have seen a macrophage demonstration as a polymorphonuclear leucocyte which had ingested lymphocytes. These macrophages come mainly from lymphatics and may be seen in sections of the intestinal wall; it is worth noting, however, that they do occur in the blood stream, for instance, the portal veins and venous spaces of the spleen pulp. In some of the *clumps* of large endothelial cells I have occasionally noted ring bodies which have the same definite outline as the nuclei of the refractile cells. These bodies were in

the cytoplasm of the endothelial cells and the nuclei of the cells were intact or were undergoing chromatolysis. It is possible that this observation may eventually throw some light on the true nature of the refractile cell.

(d) *Columnar mucous epithelial cells.* (See Fig. 25, Plate 28.) *In unstained films* isolated desquamated columnar cells or, more rarely, clumps of such cells are seen. When full of mucus the cells may be pear-shaped or rounded. The characteristic nucleus may be identified. Intact columnar epithelial cells are not very common; degenerate examples are frequently seen. *In stained films* epithelial cells, if columnar, are easily recognized. If swollen and degenerate they may be difficult to identify; a mucicarmine stain, will, however, settle the question, for when active or degenerate the cells contain mucus.

(e) *Squamous epithelial cells* from the anal margin. These large cells with characteristic, large nuclei are obvious in unstained or stained films.

(f) *Inflammatory cells—leucocytes, tissue mast cells, lymphocytes, and plasma cells.* (See Figs. 26 and 27, Plate 28.) *In unstained films* these cells are only slightly refractile. The granules in the protoplasm of the eosinophil leucocytes and mast cells are conspicuously refractile. The cells can be differentiated with certainty in stained films. Jenner's stain demonstrates the neutrophil or eosinophil granules in the leucocytes and the basophil granules in the mast cells. Unna Pappenheim's stain differentiates the plasma cells.

From the above description of vegetative entamoebae, refractile cells, and human body cells commonly found in the faeces of dysentery it will be seen that, for the identification of the entamoebae and cells, the microscopic examination of fixed stained films is a most valuable supplement to the examination of unstained material. Further, the constant checking by examination of stained films educates the eye in the best possible manner for the elucidation of unstained material.

In stained films the vegetative entamoebae and refractile cells have quite definite characteristics which serve to differentiate them from the human body cells. These characteristics similarly serve to differentiate them from other refractile bodies which may be found in the faeces. A full description of these other refractile bodies would be out of place in a paper on acute dysentery, but they deserve mention because their refractility may in unstained films cause them to be taken for vegetative entamoebae or 'refractile cells'.

These refractile bodies include :

Tetragena cysts: spherical bodies 10–15 μ in diameter containing four, clear cut, ring nuclei; each nucleus about 2 μ in diameter.

Entamoeba coli cysts: spherical bodies about 20 μ in diameter containing eight to sixteen ring nuclei; each nucleus about 3 μ in diameter.

Flagellate protozoa: when active readily recognized in unstained films by their rapid movement, arrangement of flagellae, presence or absence of undulating membrane, &c. When stationary or encysted they may be mistaken for vegetative entamoebae in the unstained film, but when stained they cannot be confused with them.

Ciliate protozoa: readily recognized by their cilia in unstained films.

Blastocysts : a rounded refractile body recognized by demilune thickenings on its rim in unstained or stained films.

Yeasts : highly refractile ; their small size distinguishes them from vegetative amoebae and body cells.

Food substances : refractile vegetable cells and fibres are easily recognized in unstained films. Starch grains may show remarkable lamellar staining in stained films. Globules of castor oil or paraffin, given as medicine, may render identification of cells impossible in unstained films ; they are excluded in a stained film. Cells of animal food substances are generally so altered in the upper digestive tract that they show as indefinite bodies with no clear outline and no clear nucleus. If unaltered they can be readily identified in a stained film.

TABLE I.

Faecal Examinations for Vegetative Entamoebae.

Month.	Total number of stools examined.	Stools containing blood and mucus, i. e. obvious dysenteric stools.	Obvious dysenteric stools containing pathogenic entamoebae.	Other types of stool, i.e. not obvious dysenterics.	Other types of stool containing pathogenic entamoebae.	Total number of stools containing pathogenic entamoebae.
June and July, 1915	47	23	16	24	6	22
August	247	127	103	120	30	133
September	283	100	77	183	23	100
October	166 [off duty 10 days]	76	68	90	22	90
November	207	98	76	109	17	93
December	159	48	35	111	19	54
January and February, 1916	20	5	4	15	1	5
Total	1129	477	379	652	118	497

Section 2. Routine Examination of Stools for Protozoa, &c.

The specimens of faeces sent to the laboratory for examination showed a great variety of macroscopical appearances. Amoebiasis was found to be so common that the clinicians looked upon all diarrhoeas with suspicion. Stools of convalescents were also sent down to be examined for cysts or the possible presence of vegetative entamoebae. Thus a great number of stools from cases which were not clinically dysenteric were examined and were compared with the stools from clinically dysenteric cases. During the period June, 1915, to February, 1916, 1,129 specimens of faeces were examined. These specimens may be divided according to their macroscopic appearance into two groups :

A. Those containing blood and mucus, i. e. clinically dysenteric
   stools 477
   Vegetative entamoebae of pathogenic type were present in
   79·4 per cent., i. e. 379

B. Other types of stool, i. e. not clinically dysenteric stools . . 652
   Vegetative entamoebae of pathogenic type were present in
   18 per cent., i. e. 118

In a mass of cases amongst which severe diarrhoeas were common it is impossible to draw a hard and fast line between dysenteric and non-dysenteric, but the cases in Group A fitted in with the clinical description of dysentery in that the patients passed frequent stools containing blood and mucus with more or less tenesmus.

The following is a short description of the types of stool met with in Groups A and B, together with a summary of the cytology, and notes based on clinical symptoms and post-mortem findings.

Group A.

Type (a). *Macroscopical.* Brown or yellow, soupy stool with numerous fragments of blood-streaked mucus or with 'sago grains' of blood-stained mucus.

Microscopical. Vegetative entamoebae numerous ; refractile cells numerous ; many inflammatory cells and a few desquamated epithelial cells.

Notes. Stools not very frequent and tenesmus not severe. Patient may complain only of diarrhoea.

An early or subacute case with lesions mainly in the upper part of the colon.

Type (b). *Macroscopical.* A scanty stool consisting entirely of blood-stained or blood-streaked muco-pus ; no faecal material.

Microscopical. Vegetative entamoebae numerous. Refractile cells numerous. A great many inflammatory cells, mainly neutrophil leucocytes ; many endothelial cells, some of which are phagocytic. A few columnar epithelial cells. Possibly also squamous epithelial cells.

Notes. Stools very frequent and severe tenesmus. Patient practically living on bed-pan. An acute or late stage with lesions involving the lower part of the large intestine.

Type (c). *Macroscopical.* Blood-stained fluid or almost pure blood, flakes of muco-pus or 'sago grains', and very little if any faecal material. May contain black cobweb sloughs.

Microscopical. Similar to type (b), save that a larger number of degenerate mucous epithelial cells may be found.

Notes. Stools very frequent and tenesmus severe. Patient may be collapsed. A late stage with severe haemorrhage and extensive sloughing of the mucous membrane.

Prognosis. A serious case, may end fatally. Such cases may, from their history, appear to be of short duration, but at the post-mortem it is obvious that the ulceration is of longer standing than the length of the history indicated.

Type (*d*). *Macroscopical.* Grass-green stool with flakes of muco-pus. Mucus very abundant, and occasionally containing blood-streaks; fragments of bright green faecal material.

Microscopical. Amoebae generally, but by no means invariably, present. Refractile cells generally present. A great many inflammatory cells, including many endothelial cells. Columnar epithelial cells numerous.

Notes. Stools not very frequent, but tenesmus severe. A subacute case with extensive ulceration and secondary inflammation.

Type (*e*). *Macroscopical.* Watery yellow orgreyish faecal fluid with little mucus and very little blood. Sometimes almost a 'rice water' stool.

Microscopical. Amoebae and refractile cells very seldom found, although inflammatory cells and epithelial cells very numerous. Relatively few red blood cells.

Notes. If any type of stool can be considered as 'probably bacillary dysentery' it is this type, and such stools occasionally yielded cultures of dysentery bacilli. Many patients first passed frequent stools containing blood, mucus, amoebae, &c., but eventually passed stools of this type. Under treatment the amoebae, blood, and mucus disappeared, but a watery purulent diarrhoea persisted for some days. In some cases this diarrhoea (four or five stools a day) proved very intractable and persisted until death. At post-mortem there was little mucous membrane left in the large intestine.

In Group B (cases not clinically dysenteric) all varieties of diarrhoeic and normal stool were met with and only two or three types are worthy of mention.

Type (*a*), extremely common.

Macroscopical. Yellow or brown diarrhoeic stool of consistence from pea soup to porridge, containing a variable amount of mucus.

Microscopical. In occasional cases a large number of vegetative entamoebae with a few red corpuscles and inflammatory cells were found. In other cases the flagellates lamblia or, more rarely, trichomonas were present; in four cases of intractable mucous diarrhoea a large ciliate, not identified, was present in great numbers. In the majority of the stools of this type there were no protozoal or body cells.

Notes. In the absence of blood to the naked eye it was found impossible to separate the stools of early or slight amoebiasis from other mucous diarrhoeas. If, on microscopical examination, there were any blood corpuscles or other body cells it was found advisable to make a lengthy search for amoebae.

Type (*b*). *Macroscopical.* Very abundant mucus with flakes of faecal material of a canary yellow colour.

Microscopical. Flagellate protozoa, *Trichomonas intestinalis*, more rarely

lamblia, very numerous.   Occasionally with lamblia a few red corpuscles and leucocytes.

Notes.   This type of diarrhoeic stool could be recognized with fair certainty macroscopically as a stool of flagellate diarrhoea.

Flagellates were frequently found together with entamoebae in many of the true dysenteric cases.   If blood corpuscles or inflammatory cells were present I always suspected an amoebic infection together with the flagellate infection. There were, however, occasional cases of intractable and recurrent mucous diarrhoea in which great numbers of lamblia were present, associated occasionally with a few blood corpuscles and leucocytes.   In these cases repeated examinations failed to reveal entamoebae.   I strongly suspect therefore that the flagellate lamblia is capable of causing intestinal inflammation, if not ulceration.

Type (c).   *Macroscopically.*   Formed or semi-formed faeces containing a large mass of extremely viscid mucus.

Microscopically.   Vegetative entamoebae never found.   Tetragena cysts occasionally present in faecal portion.   Mucus contained a great number of degenerate epithelial cells and a few inflammatory cells.

Notes.   This type of stool was frequently met with in convalescent ysenterics.

Section 3.   *Comparative Cytology of the Stools.*

All the stools in Group A (clinically dysenteric) were markedly purulent, containing a great number of inflammatory cells, chiefly neutrophil leucocytes. Endothelial cells, phagocytic and non-phagocytic, were almost invariably present. Desquamated mucous epithelial cells were not very abundant except in the type (d) and (e) stools.

In Group B (cases not clinically dysenteric) inflammatory cells were found less frequently, and if blood corpuscles and inflammatory cells were found a careful search frequently revealed entamoebae.   In fact, the presence of blood and pus in any stool made one suspect amoebiasis.   Conversely, if vegetative entamoebae were present there were always some blood corpuscles and inflammatory cells.

The examination of the stools in Group A (clinically dysenteric) was carried a step farther than the determination of the presence of entamoebae, an attempt being made to differentiate cytologically the stools of amoebic dysentery from those in the cases which were not proved to be amoebic.   Apart from the presence or absence of vegetative entamoebae there was no essential difference in the cytology.   The curious cells which I have called 'refractile cells' were found in cases of proved amoebiasis and also in cases in which amoebiasis was not proved by finding vegetative entamoebae.

I have indicated briefly (pp. 199, 200) how, by a process of exclusion, I arrived at the conclusion that 'refractile cells' were not ordinary tissue cells or inflamma-

tory cells. The next question that arises is : Are they stages in the development of the pathogenic entamoeba ? It is my opinion that they are. As regards their position in the life cycle, consultation of the writings of investigators drives one inevitably to the conclusion that there is no general agreement as to the stages of development of the pathogenic entamoeba. Two forms are recognized with certainty, the vegetative entamoeba and the tetragena cyst. There is no general agreement as to how the amoeba with one nucleus becomes a cyst with four nuclei, or as to how the four-nucleated cyst becomes a vegetative entamoeba. One candid protozoologist put it thus to me: 'We know the amoeba and we know the cyst, but we don't know for certain what happens on either side of either of them.' If one turns for assistance to the protozoologists who devote their attention to the study of pond amoebae, one again finds much confusion and no general agreement as to the complete life-history. It would, moreover, I think be a mistake to imagine that the pathogenic entamoeba must necessarily have a life-history strictly comparable to that of a pond amoeba or to the non-pathogenic entamoebae found in the frog or cockroach. The various amoeboid cells may have very diverse life-histories.

So little, therefore, being known concerning the life-history of the pathogenic amoeba, I think it is best to approach the problem with an open mind, and to avoid labelling cells with names representing stages until the progressive stages are settled. I have, therefore, refrained from endeavouring to place labels on these refractile cells corresponding to the labels given them by such authorities on amoebiasis as Rogers, Craig, and James.

In connexion with these refractile cells I would draw attention to the following publications:

1. Amoeba showing simple division, reproduction by budding. Plate 1. Haematoxylin stain. Leonard Rogers, *Dysenteries; their differentiation and treatment'*, Oxford Medical Publications, 1913.

2. Stages in the life cycle of *Entamoeba tetragena*, Figs. 23 and 24. Stages in the life-history of *Entamoeba minuta*, Fig. 27. Chas. F. Craig, *Parasitic Amoebae of Man*, Philadelphia, 1911.

3. Figures in 'Study of the Entamoebae of Man in the Panama Canal Zone', W. M. James, *Annals of Tropical Medicine and Parasitology*, July, 1914, Liverpool University Press.

4. Figures in 'Some Observations on the Effect of Emetine Administration on the Free Vegetative Forms and Cysts of Ent. Histolytica and Ent. Coli', Lieut. J. G. Thomson and Capt. D. Thomson, *Journal of Royal Army Medical Corps*, June, 1916 ; 'A Preliminary Note on the Occurrence of Peculiar " Bodies " of probably Protozoan Nature frequently found in the Stools of Dysenteric Patients', Capt. J. G. Thomson and Capt. D. Thomson, *Journal of Royal Army Medical Corps*, November, 1916.

I would draw particular attention to the curious nuclei of the refractile cells and of the vegetative entamoebae. The notable characteristic in both is a condensation of chromatin on the periphery of the nucleus or arrangement of

chromatin in a crescentic manner on the nuclear membrane. This fusiform or crescentic arrangement of chromatin on the nuclear membrane appears to me to be a remarkable feature in both the vegetative entamoeba and the refractile cell. It is possible that an endeavour to follow the development of the nucleus rather than the cell might throw fresh light on the life-history of the amoeba. The 'chromidia' which I have seen, appear to be merely these fusiform collections of chromatin on the rim of a large nucleus. This fusiform or crescentic condensation of chromatin on the rim of the nucleus is *not* commonly seen in nuclear degenerations. In degenerating nuclei, chromatin is occasionally condensed in lumps on the periphery of the nucleus, but these clean-cut crescents are, in my experience at any rate, found only in dysentery and one other disease of unknown aetiology.

Whatever stage in the cycle the refractile cells may represent, I would emphasize the importance of their association with vegetative forms in the stools, and would suggest that the criteria for diagnosis of amoebiasis be altered to include these refractile cells; or, at any rate, that the presence of these curious cells in a stained film should be considered evidence on which a course of emetine treatment should be advised.

The effect of anti-amoebic treatment on these cells is mentioned in the next section.

Section 4. Effect of Treatment on the Cytological Content of the Stools in Amoebic Cases.

It is obvious that the effect of treatment will depend not only on the details of the treatment adopted, but also on the stage of the disease which has been reached before treatment commenced.

The number of cases—thirty—upon which I had noted, more or less systematically, the effect of treatment is all too small for a general conclusion; but certain rather striking changes in the cytology were noted and are, I think, worthy of record. The treatment consisted of:

1. Flushing the large intestine by administration of magnesium sulphate mixture. Flushing repeated daily or at intervals of two or three days.

2. Injection of emetine hydrochloride, $\frac{1}{2}$ gr. twice a day, up to 6 or 10 gr. After an interval one or two further short courses of emetine injection.

3. After four to six days, bismuth mixture by the mouth three times a day.

4. Careful diet and bed. In the majority of the cases 'no diet' or 'milk diet'.

The cases chosen for observation were passing frequent stools of almost pure blood-stained muco-pus with much tenesmus.

Microscopically. Vegetative entamoebae and refractile cells were numerous. Polymorphonuclear leucocytes and other inflammatory cells were very numerous and there were some desquamated epithelial cells. The cases were not ideal cases for treatment in that they had been ill for at least a week.

After two days' treatment. Marked diminution in the number of stools.

Fluid stool containing flakes of mucus and practically no faecal material ; some of the mucous flakes blood-stained.

Microscopically. Vegetative entamoebae present. Refractile cells numerous. Less blood but quite as much pus.

After four days' treatment. Number of stools down to four or six per day ; less tenesmus. Fluid stool containing some faecal material. Much mucus and very little blood.

Microscopically. Vegetative entamoebae present, but generally of small size and not numerous ; refractile cells present. Much pus.

After six days' treatment. One to three stools a day ; little tenesmus. Fluid stool ; more faeculent ; a little mucus, but in the majority of the cases no blood.

Microscopically. Vegetative entamoebae absent. A few refractile cells found. Much pus.

In eight out of the thirty cases a watery purulent diarrhoea persisted for several days. In these eight cases vegetative entamoebae and refractile cells were still present on the sixth day, but in five cases they were not present on the eighth day.

In the remaining three cases vegetative entamoebae and refractile cells persisted in the purulent diarrhoeic stools. One case died on about the eighteenth day and vegetative entamoebae were present in sections of the intestinal wall. The other two cases recovered, but I do not know whether the entamoebae disappeared from the stools.

Thus the effect of this treatment may be summarized by saying that in the great majority of the cases entamoebae and refractile cells, blood and mucus disappear in about six days, though the stool may still be markedly purulent and remain so for many days.

The disappearance of entamoebae and refractile cells under this treatment is by no means invariable (see p. 236), so that more extensive, carefully controlled, observations are necessary before any absolute statements can be made.

Section 5. Discussion on Results of Examination of Stools.

It has been noted above that :

1. An extremely high proportion, 79·4 per cent., of the clinically dysenteric faeces contained vegetative entamoebae of pathogenic type.

2. A considerable proportion, 18 per cent., of the stools which were not clinically dysenteric contained vegetative entamoebae of pathogenic type.

From these observations I think it is justifiable to conclude that :

(*a*) At least 80 per cent. of the clinical dysenterics had amoebiasis.

(*b*) Amoebiasis was extremely common amongst the troops returning to Alexandria from the Gallipoli peninsula.

A cytological investigation of dysenteric stools revealed the presence of:

3. Well-marked purulent inflammation with relatively little catarrh of epithelial cells.

An observation of cases under treatment indicated that :

4. The purulent inflammation might persist in the absence of entamoebae.

From these observations (3) and (4) no definite conclusion can be drawn, but it seems at any rate probable that the purulent inflammation may be due to the activity of intestinal bacteria acting on the raw surface of an ulcer caused by the entamoebae.

PART V. RESULTS OF POST-MORTEM EXAMINATION.

During the period June, 1915, to February, 1916, the total number of post-mortem examinations was 168.

Twenty-six of these examinations are of no service to this paper because the examination was limited. The head alone was examined in twenty-four cases of gunshot wounds: the wound only was examined in two cases of gunshot wounds in other parts of the body.

The number of complete examinations was therefore 142
These may be divided into :
1. Dysenteric ulceration 61
     The dysenteric ulceration was associated with enterica in nine cases; with gunshot wounds in fourteen cases, and with other conditions, chiefly medical diseases, in eight cases.
2. Enterica, i.e. typhoid or paratyphoid alone 32
3. Gunshot wounds without enteric or dysenteric ulceration . . 29
4. Various conditions other than wounds and enteric or dysenteric
    ulceration 20

In the following pages, after a few remarks upon the cases in which enterica were alone present, the dysenteric lesions in the sixty-one cases are described as a whole (Section 1). The nine cases in which the dysenteric lesions were associated with enterica lesions then receive separate discussion (Section 2). Finally, the twenty-two cases in which the dysenteric lesions were associated with gunshot wounds and various conditions other than enterica similarly receive separate discussion (Section 3). In each section the cases are divided into three groups: A. Cases with vegetative amoebae in tissues. B. Cases in which amoebae of pathogenic type were found in the faeces during life but not in the tissues after death. C. Cases with no record of amoebae in faeces during life and no amoebae in tissues after death. At the end of Section 1 a note is given of the post-mortem findings in other tissues than the colon. For obvious reasons this note is confined to the thirty cases which have not the complications

TABLE II

Section 1, Group A. Cases (26) with Vegetative Entamoebae in the Tissues.

Date.	P.M. No.	Clinical Diagnosis.	Clin. Dys.	Faecal Examination.	Emetine Treat.	Cause of Death.	Dysenteric Lesions in Colon.	Scrapings for Ulcers.	Sections of Ulcers.	P. M. Diagnosis.
July 8	1	Enteric	0	Not examined	0	Haemorrhage from enteric ulcer	Isolated amoebic ulcers (b)	Not examined	Few amoebae in one ulcer	Enteric + Amoebiasis
July 19	2	Perforated gut? Enteric	?	Not examined	0	Peritonitis. Perforated amoebic ulcer	Isolated amoebic ulcers (b)	Amoebae +	Many amoebae in small ulcers	Amoebiasis
July 24	3	G.S.W. chest	Diarrhoea	Not examined	0	Peritonitis. Perforated amoebic ulcer	Confluent acute amoebic (a)	Amoebae +	Many amoebae in small ulcers	G. S. W. + Amoebiasis
Aug. 10	7	Dysentery	+++	Amoebae +	+	Exhaustion. Dysentery	Amoebic ulcerative colitis (c)	Amoebae −	Amoebae in one out of five ulcers	Amoebiasis with inflammation ++
Aug. 12	8	Abscess liver	0	Not examined	?+	Operation. Abscess liver	Scarring isolated amoebic (b)	Amoebae −	Amoebae − colon Amoebae + liver	Amoebiasis with liver abscess
Aug. 15	10	G.S.W. chest	0	Not examined	0	Empyema c. G. S. W.	Confluent acute amoebic (a)	Amoebae −	Amoebae in two out of three ulcers	G.S.W. + Amoebiasis
Aug. 17	11	Dysentery	+++	Amoebae −	+	Haemorrhage from dysenteric ulcer	Amoebic ulcerative colitis (c)	Not examined	Amoebae in one out of four ulcers	Amoebiasis with inflammation
Aug. 24	12	G. S. W. abdomen	0	Not examined	0	Peritonitis. G. S. W.	Isolated amoebic ulcers (b)	Not examined	Amoebae in all ulcers	G. S. W. + Amoebiasis
Aug. 27	13	Dysentery	+++	Amoebae +	++	Exhaustion. Dysentery	Amoebic ulcerative colitis (c)	Not examined	Amoebae in one out of four ulcers	Amoebiasis
Aug. 31	15	?	?	Not examined	?	Abscess of liver	Amoebic ulcerative colitis (c)	Amoebae +	Amoebae in all ulcers Amoebae in liver abscess	Amoebiasis with liver abscess
Sept. 1	16	G.S.W. head	0	Not examined	0	Angina pectoris	Isolated amoebic ulcers (b)	Not examined	Amoebae in one ulcer	G. S. W. + Amoebiasis
Sept. 2	17	G.S.W. chest	+++	Amoebae +	+	Empyema. G. S. W.	Bacillary inflammation (d)	Amoebae +	Amoebae in three out of four ulcers	G. S. W. + Amoebiasis with inflammation
Sept. 19	23	Dysentery	+++	Amoebae −	++	Exhaustion. Dysentery	Amoebic ulcerative colitis (c)	Not examined	Many amoebae in all small ulcers	Amoebiasis with inflammation

Date	No.	Clinical		Amoebae	Clinical Diagnosis (P.M.)		P.M. Diagnosis		Amoebae	Sections of Ulcers	Final
Sept. 25	27	G.S.W. head	+	Amoebae+	Meningitis. G.S.W.	+	Isolated amoebic ulcers	(b)	Amoebae+	Not examined	G.S.W. + Amoebiasis
Oct. 3	29	Cirrhosis of liver	0	Not examined	Br-pneu. with cirrhosis of liver	0	Isolated amoebic ulcers	(b)	Amoebae+	Not examined	Cirrhosis liver + Amoebiasis
Oct. 17	30	Enteric + Dysentery	++	Amoebae+	Para B + Dysentery	++	Amoebic ulcerative colitis	(c)	Not examined	Amoebae in two out of four ulcers	Enteric + Amoebiasis
Oct. 19	31	Diabetes	0	Not examined	Diabetic coma	0	Isolated amoebic ulcers	(b)	Amoebae+	Many amoebae in all ulcers	Diabetes + Amoebiasis
Oct. 26	34	Dysentery	+++	Not examined	Exhaustion. Dysentery	?+	Bacillary inflammation	(d)	Not examined	Many amoebae in small ulcers	Amoebiasis with septicaemia
Nov. 6	38	Dysentery	++	Amoebae+	Exhaustion. Dysentery	+	Isolated amoebic ulcers	(b)	Not examined	Many amoebae in all ulcers	Amoebiasis with septicaemia
Nov. 13	42	G.S.W. buttock	Diarrhoea	Not examined	Septicaemia from G.S.W.	0	Isolated amoebic ulcers	(b)	Amoebae+	Many amoebae in all ulcers	G.S.W. + Amoebiasis
Nov. 14	43	Operation, cholecystectomy	+	Amoebae+	Peritonitis from operation	+	Isolated amoebic ulcers	(b)	Not examined	Few amoebae in small ulcers	Operation + Amoebiasis
Nov. 21	46	Enteric + Dysentery	++	Amoebae+	Exhaustion. Dysentery	+++	Bacillary inflammation	(a)	Not examined	Many amoebae in all ulcers	Enteric + Amoebiasis with inflammation
Nov. 27	50	G.S.W. foot	0	Not examined	Septicaemia c. G.S.W.	0	Isolated amoebic ulcers	(b)	Not examined	Many amoebae in all ulcers	G.S.W. + Amoebiasis
Dec. 2	52	G.S.W. chest	0	Not examined	Empyema c. G.S.W.	0	Isolated amoebic ulcers	(b)	Not examined	Many amoebae in all ulcers	G.S.W. + Amoebiasis
Dec. 13	53	Appendicitis	+	Amoebae+	Haemorrhage from dys-enteric ulcer	?+	Amoebic ulcerative colitis	(c)	Not examined	Many amoebae in all ulcers. Amoebae in liver abscess	Amoebiasis with liver abscess
Jan. 2	58	G.S.W. legs	+	Amoebae+	Septicaemia from G.S.W.	?+	Isolated amoebic ulcers	(b)	Not examined	Many amoebae in all ulcers	G.S.W. + Amoebiasis

Under 'Clinical Dysentery', I have indicated severe cases by +++ and mild cases by +.
Under 'Emetine Treatment', + indicates less than 5 gr. of emetine hydrochloride injection: ++ indicates from 5 to 10 gr.: +++ indicates more than 10 gr.
Under 'Dysenteric Lesions in Colon', I have indicated the types of colic ulceration which are fully explained in the later text.
Under 'Sections of Ulcers', I have indicated roughly the frequency of amoebae in the tissues.
Under 'P. M. Diagnosis', I have indicated those cases which are discussed in Sections 2 and 3 and also the cases wherein amoebiasis was complicated by septicaemia of intestinal origin, liver abscess, &c.

of the cases in Sections 2 and 3.   Here also is given a summary of the causes of death in dysenteric ulceration.

Amongst the cases of enteric it was common to find a rather extensive involvement of the follicles in the large intestine.   This extensive involvement of the large intestine was more common than in the cases of enteric which I have met with in England.   In only one case did I have difficulty in deciding whether an involvement of the large intestine should be classed as enteric or dysenteric ulceration.   This case proved on microscopical examination to be apparently a pure enteric; it is therefore not included in the dysenteric cases.   I have made a thorough examination of a large number of the colic ulcers which I had no hesitation in classing as enteric involving the large intestine; the naked-eye diagnosis is supported by the microscopical findings.

Section 1.   *All Cases* (61) *in which there was Dysenteric Ulceration of the Colon.*

Group A.   Cases (26) *with vegetative entamoebae in the tissues.*   The lesions found on the inner surface of the large intestine may be classified and described as follows:

1. *Minute nodules with an injected margin.*   These lesions are generally about the size of a pin-head, and the intestine must be examined carefully in order to see them.

Microscopically.   The histology is similar to that of (2) save that the mucosa is not ulcerated.

2. *Minute nodules with a yellow necrotic or ulcerated centre and injected margin.*   These lesions are also very minute.   The appearance is very similar to that seen in 'follicular ulceration' of the colon, which is occasionally found in diarrhoea and vomiting of infants.

Microscopically.   There is a small area wherein the mucosa and muscularis mucosae have been necrosed and cast off.   The superficial submucosa, immediately beneath the muscularis mucosae, shows serous exudate, haemorrhage, and fibrin formation.   The haemorrhage is well marked, and is more extensive than the size of the lesion would lead one to expect.   The nuclei of the tissue cells in the affected area show chromatolysis, but collagen fibres are well stained.   There is slight infiltration with lymphocytes, plasma cells, and a few neutrophil leucocytes. A few vegetative entamoebae may be found in the area of serous exudate, but they may be absent.   The veins are moderately dilated.   They may contain desquamated endothelial cells and fibrinous thrombi containing neutrophil leucocytes.   Others may contain clumps of desquamated endothelial cells mixed with red corpuscles.   Occasionally refractile cells and vegetative entamoebae may be found within the veins.   The walls of some of the larger veins show definite changes.   The endothelium is absent, and the tissues of the wall are rarified and degenerated.   The tissue elements appear to be separated from each

other by oedema. Amoebae may occasionally be found in the degenerated wall.

3. *Larger nodules and 'bouton de chemise' ulcers* (diagnostic of amoebic dysentery). (See Plates 30 and 31.) These lesions vary in size from 0·5 to 1·5 cm. in diameter. The nodule may be covered by intact congested mucous membrane ; on section gelatinous yellow débris is found in the submucosa. In the slightly more advanced lesion the mucosa and muscularis mucosae at the summit of the lesion are ulcerated and some of the débris has escaped, leaving a small depressed centre with a raised margin—' bouton de chemise' ulcer. (See letter A in Plate 31.) If this ulcer is situated on the summit of a fold of mucous membrane it is frequently transverse and slit-shaped. On section through the ulcer it is found to involve, as a rule, the whole thickness of the submucosa and to extend laterally beneath the mucosa. At the edges of the ulcer the submucosa is markedly thickened, and prominent vessels are seen in the thickening. There is gelatinous yellow or grey débris in the base and under the margins of the ulcer. The muscle coat may be slightly involved in the necrosis. This lesion appears to be primarily situated in the deeper part of the submucosa and attains a relatively large size before the mucosa breaks down to form the ulcer.

Microscopically. The ulcer leads down to a mass of necrotic débris in the submucosa, which extends widely beneath intact mucosa and muscularis mucosae at the edge of the ulcer. The débris in the base and beneath the edges of the ulcer is markedly haematoxyphil. It consists of dead tissue cells and fibrils, collagenous and elastic, together with inflammatory cells. The ghosts of thrombosed vessels may be seen in the débris, and pyknotic nuclei of poly-morphonuclear leucocytes are numerous. There is occasionally some fibrin containing red corpuscles in the débris. The neighbouring submucous tissues and, to a less extent, the mucosal and muscular tissues show serous exudation with fibrin formation and some red corpuscles. The thickening of the submucosa is mainly due to this haemorrhagic exudate. The tissue cells within this area of exudation are generally swollen and degenerate, and their nuclei show chromatolysis. The bundles of collagen fibres are separated by the exudation, but are stained well. The muscle cells may be swollen and their nuclei may show chromatolysis. The submucous, mucosal, and muscular tissues around the necrotic focus show infiltration with lymphocytes, plasma cells, a few neutrophil leucocytes, and some mast cells. This infiltration with inflammatory cells is not very dense. It is best seen around the blood-vessels and in the tissues immediately beneath the muscularis mucosae. It is generally present, however, to a slight degree at a considerable distance from the lesion. In this stage there is seldom much proliferation of fibroblasts or capillary endothelial cells. In the damaged tissues around the necrotic focus vegetative entamoebae are found. Occasionally they are very numerous, but as a rule it is necessary to search with some care. They are frequently found in the submucosa at a considerable distance from the lesion, even beyond the area of cellular infiltration ; they may also be present in the muscle and subserosa ; more rarely they may be found in

the mucosa.   Occasionally masses of entamoebae may be found in the fibrous
septa of the muscle coat.   An observation of importance is that they may be
surrounded by quite intact tissues in which there is no inflammatory reaction.
The veins are markedly dilated ; this dilatation is widespread, involving sub-
serous as well as submucous and mucous vessels.   These dilated veins occasionally
contain fibrinous thrombi enclosing neutrophil leucocytes.   In some veins clumps
of desquamated endothelial cells may be seen.   Vegetative entamoebae and, more
rarely, refractile cells may be present within the veins.   The walls of the larger
veins at a distance from the lesion frequently show definite changes.   The
endothelium is absent and the tissues of the wall are rarefied by oedema.   In the
more advanced stages the wall is destroyed and, occasionally, vegetative enta-
moebae may be found in the damaged wall.   Amoebae are numerous in the
perivascular tissues around these damaged vessels.   The lymphatics are frequently
full of inflammatory cells and desquamated endothelial cells ; the endothelial
cells are frequently phagocytic.   Vegetative entamoebae are rarely found in the
larger lymphatics.

4. *Undermined rounded or transverse oval ulcers.*   (See letter B, Plate 31.)
In later stages larger ulcers are found ; these may be of considerable size ; they
may even encircle the lumen of the gut.   They are well defined ; their margin
is raised and undermined.   In the base there is frequently some ragged lemon
yellow or greyish yellow débris, but occasionally the base is formed by clean
muscularis or subserosa.   When the base is clean the ulcers do not project from
the surrounding mucosa.

Microscopically.   These ulcers are merely a further stage of the ' bouton de
chemise ' ulcer ; the changes seen microscopically are similar, save that the
muscle is more frequently and more extensively involved and the cellular
infiltration is more marked.   Polymorphonuclear leucocytes are more numerous.
Amoebae are generally present, but not in such numbers as in lesions of the
previous type.   Sections of the clean ulcers may fail to demonstrate their
presence.

5. *Confluent ulceration* is of two forms, which depend on the density and
mode of spread of the initial lesions in a given area of gut.

Form (*a*) (see Plate 31) is produced by close-set lesions of the third type.   If
the button lesions are set close together, a confluent ulcer may result which has
ragged depressions in its base, so that the base has a honeycomb appearance.
(See letter B, Plate 31.)

The remnants of mucosa between these confluent ulcers may necrose, and
most of it slough, so that the affected area has an extremely ragged villous
surface.   (See lower drawing, Plate 31.)   The latter process may involve the
whole caecum and ascending colon ; the muscle may be involved in the necrosis
and the whole wall may be friable.   Such lesions may perforate intraperitoneally
or extraperitoneally, or may give rise to peritonitis without a visible breach of
the necrotic tissue.

Microscopically.   This advanced stage may be difficult to recognize as

amoebic. The whole of the tissues are more or less necrotic and full of bacilli. Amoebae may not be found. There is extensive haemorrhage, vessels are thrombosed, and there is much infiltration by neutrophil leucocytes.

Form (b) (see Plates 32 and 33) is produced by confluence of lesions of a more sparsely scattered type. Thus the isolated transverse oval ulcers of the fourth type may have spread until they meet, leaving islands of mucous membrane. The lesions spread and unite chiefly beneath the mucosa. Very extensive separation of mucosa from the muscle is therefore seen. (See Plate 33.) A probe may be passed under bridges of mucosa from ulcer to ulcer: this is especially the case when the ulcers are clean based. In some specimens large tracts of mucosa, completely separated in this manner from the muscularis, are perforated like a sieve by holes corresponding to the initial ulceration. In other cases there is much inflammation of the edges and floor of the ulcers, so that thick infiltrated islands and bands of mucosa and submucosa alternate with deep ulcers which may reach the muscle coat. The latter appearance cannot be distinguished from that seen in ' ulcerative colitis ' of the sporadic type met with in England. (See Plate 32.)

Microscopically. The edges of the ulcers may be markedly undermined. Inflammatory changes are very severe. Cellular infiltration is widespread and polymorphonuclear leucocytes are numerous. There is much proliferation of fibroblasts and capillary endothelial cells. Amoebae are practically never found. Veins are very frequently thrombosed and lymphatics greatly inflamed. The venous thrombosis and lymphangitis leads to further death of tissues, and eventually large areas of gut may be entirely denuded of mucosa.

6. *Amoebic ulceration combined with diphtheroid inflammation.* (See Plate 34.) Ulceration of any of the above types, more especially of the advanced types, may be combined with intense haemorrhage, mainly submucous, and diphtheroid inflammation. The diphtheroid inflammation affects the edges of the ulcers and the surrounding mucosa. Thus the clean-cut appearance of the amoebic ulcer is obscured. The greenish diphtheroid membrane may cover the floor of the ulcer, whilst large areas of mucosa at a distance from the ulcer may show a thick green diphtheroid membrane on the surface (' bacillary dysentery ').

Microscopically. Sections through the ulcers show a marked involvement of the submucosa. In the base of the ulcer is some débris containing fibrin and polymorphonuclear leucocytes. All the surrounding tissues show much haemorrhage, fibrin formation, and a dense cellular infiltration. The infiltrating cells are mainly of the lymphocytic group, but near the necrotic surface there is marked infiltration with neutrophil leucocytes. In the tissues and vessels vegetative entamoebae may be found. Thrombosis of dilated veins is common, and the lymphatics are packed with cells. There is proliferation of fibroblasts and endothelial cells.

Sections through an area of diphtheroid inflammation at a distance from the ulcer show that the greenish membrane on the surface consists of necrotic

superficial mucosa, fibrin, and remnants of polymorphonuclear leucocytes. Beneath this the thick infiltrated wall of the gut shows serous exudation. The haemorrhage is most marked in the submucosa, but may involve all coats of the intestine and the mesenteric tissues. There is much diffuse infiltration with lymphocytes and plasma cells, and close to the necrosing surface a marked infiltration with neutrophil leucocytes. In the tissues and lymphatics is a remarkable number of phagocytic endothelial cells. The phagocytes contain red corpuscles and blood pigment, and also inflammatory cells. Endothelial cells enclosing red corpuscles are especially numerous around the blood-vessels. The veins and capillaries are greatly dilated. They contain many neutrophil leucocytes. They are occasionally thrombosed, and frequently contain desquamated endothelial cells. The vessel walls may show degeneration changes similar to those mentioned above. There is some lymphangitis. Vegetative entamoebae are not found. This microscopic appearance corresponds to that of ' bacillary dysentery '. Sections stained by Twort's method or Weigert's Gram method show masses of bacteria in the necrotic tissues and also in the deeper parts of the intestinal wall. The bacteria are, for the most part, large Gram positive bacilli. Gram negative bacilli resembling B. coli are present in the membrane, but are not numerous ; they are not found in the deeper tissues.

7. *Healing and scarring ulcers.* Lesions representing healing or healed ulcers of types 1 and 2 were not detected. Ulcers of larger size were observed with puckered edges, a smooth pigmented base, and pigmented serosa. In one or two cases extensive, smooth, pigmented areas were found crossing the lumen of the gut transversely. No cases of serious constriction of the lumen by scarring were found.

Microscopically. A granulation tissue is formed by the vascular submucosa, and epithelium grows over from the mucosa. The overhanging fragments of mucosa at the edge of the ulcer are frequently included in the scar tissue, leading to the formation of mucous cysts in the submucosa.

In the above description and classification of the lesions in the large intestine I have endeavoured to indicate how the amoebic lesions may, by their age, and by their density or scarcity in a given area of gut, produce a great variety of appearances.

I have also endeavoured to indicate the important influence inflammatory changes have upon the picture. The degree of these inflammatory changes varied greatly in individual cases. Occasionally when the amoebic lesions were advanced there was relatively little inflammatory reaction, but in other cases the inflammatory changes were so severe that the amoebic lesions were very atypical in macroscopic and microscopic appearances. It is reasonable to assume, therefore, that these inflammatory changes are not caused by the amoebae. They appear to be complicating inflammations, which result from varying degrees of bacterial infection when an ulcerated or necrotic surface is exposed to the action of the intestinal contents.

It is obvious that the general appearance of the large intestine in the post-mortem room will depend not only on the nature of the predominating amoebic lesion and the extent of the secondary inflammation, but also on the distribution of both in the length of the large intestine.   In these twenty-six cases *the lesions were distributed as follows* :

Throughout the large intestine	12 cases.
Throughout colon but not rectum	3 ,,
Descending colon and rectum only. . . .	3 ,,
Caecum, ascending colon, and sigmoid only . .	3 ,,
Descending colon only	2 ,,
Caecum and ascending colon only	3 ,,

Site of the most advanced lesion :

Sigmoid colon	12 ,,
Caecum	9 ,,
Sigmoid and caecum equally affected . . .	5 ,,

A classification of the large intestines in these twenty-six cases of Group A, based on the predominating type of amoebic lesion, the distribution of the amoebic lesions in the length of the large intestine, and the extent of the inflammatory changes, gives the following result :

(*a*) Widespread and confluent acute amoebic ulceration.   Lesions of type 5 *a* predominating   .   .   .   .   .   .   2 cases.

(*b*) Isolated rounded or oval amoebic ulcers.   Lesions of type 3, 4, or 7 predominating, with wide areas of intact mucosa between the lesions or groups of lesions, i.e. text-book appearance of subacute amoebic dysentery   .   .   .   14 ,,

(*c*) Widespread confluent ulceration.   Lesions of type 5 *b* predominating, leading to transverse ulcers with islands and bridges of mucous membrane between the ulcers, i.e. 'ulcerative colitis' of the sporadic English type   .   .   7 ,,

(*d*) Haemorrhage, mainly submucous, with diphtheroid membrane on mucosa obscuring typical amoebic ulcers.   Lesions of type 6 predominating, i.e. amoebic ulceration obscured by 'bacillary dysentery' type of inflammation   .   .   .   3 ,,

Thus it can be said that the appearances, macroscopic and microscopic, varied from those described in the text-book as typical of acute and subacute amoebic dysentery, through all the stages of sporadic ulcerative colitis of the English type, to an appearance similar to that described as typical of acute bacillary dysentery.   The only feature common to all the cases, with one exception, was the presence somewhere or other in the large intestine of a button or small ulcer, in the tissues of which, on microscopical investigation, vegetative entamoebae were found.   In the one exception amoebae were not found in the colic ulcers, which were healing, but were present in a liver abscess.

TABLE III

Group B. Cases (21) in which Entamoebae of Pathogenic Type were found in the Faeces during Life but not in the Tissues after Death.

Date.	P. M. No.	Clinical Diagnosis.	Clin. Dys.	Faecal Examination.	Emetine Treat.	Cause of Death.	Dysenteric Lesions in Colon.		Scrapings for Ulcers.	Sections of Ulcers.	P. M. Diagnosis.
July 28	4	Enteric + Dysentery	+++	Amoebae+	+++	Exhaustion. Dysentery	Isolated amoebic ulcers	(b)	Not examined	Deep ulcers	Enteric + Amoebiasis with inflammation
Aug. 5	5	Dysentery	+++	Amoebae+	++	Exhaustion. Dysentery	Bacillary inflammation	(d)	Amoebae−	Deep ulcers	Amoebiasis with inflammation
Aug. 9	6	Dysentery	+++	Amoebae+	+++	Exhaustion. Dysentery	Isolated amoebic ulcers	(b)	Not examined	Not examined	Amoebiasis
Aug. 28	14	Dysentery	+++	Amoebae+	++	Exhaustion. Dysentery	Bacillary inflammation	(d)	Amoebae−	Deep ulcers	Amoebiasis with inflammation
Sept. 3	18	Dysentery with hepatitis	+++	Amoebae+	+++	Haemorrhage following operation	Amoebic ulcerative colitis	(c)	Amoebae−	Granulating ulcers	Amoebiasis healing
Sept. 4	19	G. S. W. spine	+++	Amoebae+ (2)	++	Septicaemia. G. S. W.	Isolated amoebic ulcers	(b)	Not examined	Undermined ulcers	G. S. W. + Amoebiasis with inflammation
Sept. 13	20	Enteric + Dysentery	+++	Amoebae+	+++	Typhoid Pyaemia	Bacillary inflammation	(d)	Not examined	Deep ulcers	Enteric + Amoebiasis with inflammation
Sept. 18	21	G. S. W. neck	+ (cured)	Amoebae+	+++ (cured)	Gangrene of lung	Isolated amoebic ulcers	(b)	Amoebae−	Not examined (healed)	G. S. W. + Amoebiasis healed
Sept. 18	22	Dysentery	+++	Amoebae+	+	Exhaustion. Dysentery	Confluent acute amoebic	(a)	Not examined	Undermined ulcers	Amoebiasis
Sept. 20	24	Dysentery	+++	Amoebae+	+	Exhaustion. Dysentery	Bacillary inflammation	(d)	Not examined	Deep ulcers	Amoebiasis with inflammation

Date	No.	Clinical Dysentery	Emetine Treatment	Dysenteric Lesions in Colon	Sections of Ulcers	Clinical result	P. M. Diagnosis		Amoebae	Ulcer type	Final diagnosis
Sept. 21	26	Dysentery	+++	Amoebae+ (2)	+++	Br. - pneu. Dysentery	Amoebic ulcerative colitis	(c)	Amoebae -	Granulating ulcers	Amoebiasis healing
Sept. 28	28	Lobar pneumonia	++	Amoebae+	++	Lobar pneumonia	Amoebic ulcerative colitis	(c)	Not examined	Undermined ulcers	Lobar pneumonia +Amoebiasis
Oct. 25	33	Enteric + Dysentery	+++	Amoebae+	++	Exhaustion. Dysentery	Amoebic ulcerative colitis	(c)	Not examined	Undermined ulcers	Enteric + Amoebiasis
Nov. 4	37	G.S.W. femur	+++	Amoebae+	++	Exhaustion. Dysentery	Amoebic ulcerative colitis	(c)	Not examined	Undermined ulcers	G.S.W. + Amoebiasis with inflammation
Nov. 7	39	Dysentery	+++	Amoebae+	++	Br. - pneu. Dysentery	Amoebic ulcerative colitis	(c)	Not examined	Deep ulcers	Amoebiasis with inflammation
Nov. 10	40	Enteric + Dysentery	+++	Amoebae+	++	Br. - pneu. Enteric	Isolated amoebic ulcers	(b)	Not examined	Granulating ulcers	Enteric + Amoebiasis healing
Nov. 26	48	Dysentery	+++	Amoebae+	++	Br. - pneu. Jaundice	Isolated amoebic ulcers	(b)	Not examined	Granulating ulcers	Amoebiasis healing
Dec. 1	51	Dysentery	+++	Amoebae+	+	Exhaustion. Dysentery	Bacillary inflammation	(d)	Not examined	Deep ulcers	Amoebiasis with inflammation
Dec. 15	54	Dysentery	++	Amoebae+	++	Exhaustion. Dysentery	Isolated amoebic ulcers	(b)	Amoebae -	Granulating ulcers	Amoebiasis healing
Dec. 20	56	Dysentery + Enteric	+++	Amoebae+ (2) Amoebae- (1)	++	Haemorrhage from dys-enteric ulcers	Confluent acute amoebic	(a)	Not examined	Undermined ulcers	Enteric + Amoebiasis
Jan. 30	60	Appendicitis	++ (cured)	Amoebae+	+++ (cured)	Intestinal obstruction	Isolated amoebic ulcers	(b)	Not examined	Granulating ulcers	Appendicitis + Amoebiasis healing

Under ' Clinical Dysentery ', I have indicated severe cases by +++ and mild cases by +.
Under ' Emetine Treatment ', + indicates less than 5 gr. of emetine hydrochloride injection ; ++ indicates 5–10 gr. ; +++ indicates more than 10 gr.
Under ' Dysenteric Lesions in Colon ', I have indicated the types of colic ulceration which have been fully explained in the previous text.
Under ' Sections of Ulcers ', I have indicated roughly the characteristics of the ulceration.
Under ' P. M. Diagnosis ', I have indicated the cases which are further discussed in Sections 2 and 3 and also the cases wherein the amoebic ulceration was complicated by severe inflammation and the cases wherein the ulcers were healing or healed.

In one-half of the cases vegetative entamoebae were numerous, being readily demonstrated in nearly all the ulcers taken for section. In the rest of the cases a more prolonged search was necessary, and care had to be taken in selecting the most suitable type of lesion, i. e. the smaller lesions. In the areas of confluent ulceration complicated by severe inflammation it was generally impossible to demonstrate amoebae, but in one such case, complicated by severe haemorrhagic inflammation, entamoebae were very numerous in all the sections of the deeper ulcers.

Group B.   Cases (21) of dysentery in which vegetative amoebae of pathogenic type were found in the faeces during life but not in the tissues after death.   The macroscopic lesions on the inner surface of the large intestine resembled those in Group A.

A classification similar to that adopted in Group A (p. 217) gave the following result :

    (*a*) Widespread confluent acute amoebic ulceration   .   .   .   2 cases.

    (*b*) Isolated lesions or groups of lesions, i. e. typical subacute
        amoebic   .   .   .   .   8 „
                                     (5 healing or healed)

    (*c*) Widespread confluent ulceration.   ' Ulcerative colitis ' type .   6 cases.

    (*d*) Haemorrhage, with diphtheroid membrane obscuring isolated
        lesions, i. e. bacillary dysentery type of colon   .   .   .   5 „

In this group, therefore, when compared with Group A :

No amoebae were found in the tissues. (In Cases 6 and 21 the material preserved for microscopic investigation was lost.) There were relatively few cases showing the isolated lesions or groups of lesions (*b*) in which amoebae were readily found in Group A.

In no less than five of the eight cases showing such isolated lesions the lesions were healing or healed.

A greater proportion of the cases showed lesions of amoebic type complicated by severe inflammation, (*c*) and (*d*).

An explanation of these special features can be formed by comparing the amount of specific treatment indicated in the tables of Group A and Group B and by a reference to the effects of treatment (p. 236).

In this Group B specific treatment had been given in all cases, and this treatment was, in general, much more thorough than in Group A. The absence of amoebae from the tissues and the presence of healing and healed amoebic lesions indicate that the treatment was successful. In two cases, indeed, the amoebic dysentery was considered in the wards to have been cured.

The preponderance of confluent lesions, and lesions complicated by severe inflammation, agrees with the observation (p. 208) that specific treatment may remove amoebae, but a purulent non-amoebic inflammation of the affected bowel may persist.   ·

TABLE IV

Group C.   Cases (14) with no Record of Amoebae in Faeces during life and

TABLE IV

Group C. Cases (14) with no Record of Amoebae in Faeces during Life and no Amoebae in Tissues after Death.

Date.	P. M. No.	Clinical Diagnosis.	Clin. Dys.	Faecal Examination.	Emetine Treat.	Cause of Death.	Dysenteric Lesions in Colon.	Scrapings.	Sections of Ulcers.	P. M. Diagnosis.
Aug. 12	9	Dysentery	+++	Not examined	++	Exhaustion. Dysentery	Pure bacillary inflammation	Not examined	Inflammation	Pure bacillary dysentery
Sept. 21	25	Dysentery	+++	Amoebae-	++	Exhaustion. Dysentery	Amoebic ulcerative colitis (c)	Not examined	Undermined ulcers	Amoebiasis
Oct. 22	32	Dysentery	+++	Amoebae- (3) Not examined	++	Haemorrhage from dysenteric ulcer	Amoebic ulcerative colitis (c)	Not examined	Undermined ulcers	Amoebiasis with inflammation
Oct. 27	35	Dysentery	+++	Not examined	+++	Exhaustion. Dysentery	Amoebic ulcerative colitis (c)	Not examined	Undermined ulcers	Amoebiasis with inflammation
Nov. 2	36	Lobar pneumonia	0	Not examined	0	Lobar pneumonia	Isolated amoebic ulcers (b)	Not examined	Granulating ulcers	Lobar pneumonia + amoebiasis healing
Nov. 12	41	Dysentery?	++?	Not examined	+	Haemorrhage from dysenteric ulcer	Pure bacillary inflammation	Not examined	Inflammation	Pure bacillary dysentery with septicaemia
Nov. 14	44	Dysentery	+	Amoebae-	+	Haemorrhage from dysenteric ulcer	Pure bacillary inflammation	Not examined	Inflammation	Pure bacillary dysentery
Nov. 20	45	Dysentery	++	Not examined	+	Exhaustion. Dysentery	Pure bacillary inflammation	Not examined	Inflammation	Pure bacillary dysentery
Nov. 26	47	G.S.W. thigh	++	Not examined	++	Sepsis. G. S. W.	Isolated amoebic ulcers (b)	Amoebic-	Granulating ulcers	G. S. W. + amoebiasis healing
Nov. 27	49	Enteric	?	Not examined	?	Perforated dysenteric ulcer	Amoebic ulcerative colitis (c)	Amoebic-	Undermined ulcers	Enteric + amoebiasis
Dec. 16	55	Dysentery	+++	Not examined	++	Exhaustion. Dysentery	Isolated amoebic ulcers (b)	Not examined	Granulating ulcers	Amoebiasis healing with inflammation
Dec. 27	57	Meningitis	0	Not examined	0	Hydrocephalus, &c.	Isolated amoebic ulcers (b)	Not examined	Granulating ulcers	Meningitis + amoebiasis healing
Jan. 8	59	Frost-bite	0	Not examined	0	Br. pneu. with abscess lung	Isolated amoebic ulcers (b)	Not examined	Granulating ulcers	Frost-bite + amoebiasis healing
Feb. 13	61	Dysentery	+++	Not examined	++	Lobar pneumonia	Pure bacillary inflammation	Not examined	Inflammation	Pure bacillary dysentery with septicaemia

Under 'Clinical Dysentery', I have indicated severe cases by +++ and mild cases by +.
Under 'Emetine Treatment', + indicates less than 5 gr. of emetine hydrochloride injection; ++ indicates 5-10 gr.; +++ indicates more than 10 gr.
Under 'Dysenteric Lesions in Colon', I have indicated the types of colic ulceration which have been fully explained in the previous text and also the cases in which there was only a superficial inflammation.
Under 'Sections of Ulcers', I have indicated roughly the characteristics of the ulceration.
Under 'P. M. Diagnosis', I have indicated the cases which are further discussed in Sections 2 and 3 and also the cases in which there was 'pure bacillary dysentery'.

In these twenty-one cases *the lesions were distributed as follows* :

Throughout the large intestine	15 cases.
Throughout colon but not rectum	3 ,,
Caecum, ascending colon, and sigmoid only	3 ,,

Site of most advanced lesion :

Sigmoid colon	10 ,,
Caecum	2 ,,
Sigmoid and caecum equally affected	9 ,,

Group C. Cases (14) with no record of amoebae in faeces during life and no amoebae in tissues after death.

In this group there were only nine cases showing amoebic lesions of the types described in Group A.

A classification similar to that adopted in Group A gives the following result :

(*b*) Isolated lesions or groups of lesions, i.e. typical subacute amoebic . . . . 5 cases.
(*c*) Widespread confluent ulceration, i.e. ulcerative colitis type . 4 ,,

In only one case is there a record of examination of the faeces ; amoebae were not found, although they were examined on three separate occasions.

In these nine cases *the lesions were distributed as follows* :

Throughout the large intestine	2 cases.
Throughout the colon but not rectum	3 ,,
Sigmoid and rectum only	3 ,,
Caecum only	1 ,,

The sites of the most advanced lesion were :

Sigmoid colon	4 ,,
Caecum	1 ,,
Caecum and sigmoid equally affected	2 ,,
Transverse colon	2 ,,

In the remaining five cases there were no amoebic lesions of any of the types described in Group A. The whole large intestine showed intense submucous haemorrhage with a greenish diphtheroid membrane in the mucosa, or a shallow serpiginous ulceration involving the superficial part of the mucosa.

The appearance, therefore, resembled that of the inflammation which complicated the amoebic lesions in cases of 'the bacillary dysentery type'. In these five cases, however, there were no amoebic lesions such as have been described. The appearance was that of a 'pure bacillary dysentery'.

Comparison of certain histological changes in these cases with changes in

early lesions of acute amoebic dysentery has made me suspect that there was an amoebic lesion underlying the bacterial infection. My material has not, however, enabled me to demonstrate this. The cases are, therefore, regarded in this paper as pure bacterial inflammation.

The only evidence that this bacterial inflammation was caused by bacilli of the dysenteric group was a positive agglutination to Shiga bacilli, during life, in Case No. 61; in this case bacilli coli were also cultivated from the blood (Lieut. Magner) three days before death. In Case No. 9 the serum failed to agglutinate Shiga and Flexner strains of dysenteric bacilli. In Case No. 41 an extremely motile Gram negative bacillus, giving the sugar reactions of a para-typhoid bacillus, was cultivated from the spleen at post-mortem by Lieut. Magner; this organism was not, however, agglutinated by paratyphoid A or B sera. Further, the serum of this case did not agglutinate Shiga or Flexner bacilli. The other two cases had not been subjected to bacteriological and serological investigation.

In only one case is there a record of examination of the faeces for protozoa. Amoebae were not found. Making a tentative diagnosis on morbid anatomical grounds only, I shall call these cases examples of ' pure bacillary dysentery '. In all five cases the lesions were distributed throughout the large intestine: in all five cases the most advanced lesion was present in the sigmoid colon.

Summary of post-mortem findings in the large intestine of sixty-one cases of dysenteric ulceration.

A classification based on the morbid anatomical appearances gives the following result:

I. Amoebic dysentery.
    (a) Widespread confluent acute amoebic ulceration . . 4 cases.
    (b) Isolated amoebic lesions or groups of lesions . . . 27 ,,
    (c) Widespread confluent transverse amoebic ulcers, 'ulcera-
        tive colitis type' . . . . 17 ,,
    (d) Bacillary type of inflammation obscuring amoebic lesions 8 ,,

II. Non-amoebic dysentery.
    Pure bacillary type of inflammation . . . . . 5 ,,

Distribution of lesions in the large intestine:

I. Amoebic dysentery.
    Throughout the large intestine . . . . 29 cases.
    Throughout colon but not rectum . . . . 9 ,,
    Descending colon and rectum only . . . . 6 ,,
    Descending colon only . . . . . . 2 ,,
    Caecum, ascending colon, and sigmoid only . . 6 ,,
    Caecum and ascending colon only . . . . 4 ,,

II. 'Pure bacillary' dysentery.

    Throughout the large intestine .   .   .   .   5 cases.

Site of the most advanced lesion:

I. Amoebic dysentery.

    Sigmoid colon   .   .   .   .   .   . 26 ,,

    Caecum .   .   .   . 12 ,,

    Sigmoid and caecum equally affected .   .   . 16 ,,

    Transverse colon .   .   .   .   .   .   2 ,,

II. 'Pure bacillary' dysentery.

    Sigmoid colon   .   .   .   .   .   .   5 ,,

The large intestines of types (*a*), (*b*), and (*c*) presented no difficulty in diagnosis in the post-mortem room. Types (*a*) and (*b*) are those described in the text-books as typical of amoebic dysentery. Type (*c*) is sometimes described as amoebic and sometimes as bacillary, but I had previously seen cases of amoebiasis in the London Hospital post-mortem room which were indistinguishable from cases of 'sporadic ulcerative colitis'. I was, therefore, fully prepared to find amoebae in the smaller lesions, or in the faeces of this type of intestine. Thus, in forty-eight cases there was no real difficulty in diagnosis. It was, however, confusing to find amoebae in the faeces or in sections of gut in eight cases when the predominating appearance was definitely that of acute bacillary dysentery. I have diagnosed, tentatively, these eight cases as amoebic complicated by bacillary dysentery, though the bacillary infection was not proved by serological or bacteriological investigation. The five cases without amoebic lesions I have diagnosed, tentatively, as pure bacillary dysentery, though in these, apart from one positive agglutination to Shiga bacilli, proof of infection by bacilli of the dysenteric group is absent.

Allowing the above tentative diagnosis of 'bacillary dysentery', the sixty-one cases of dysenteric ulceration of the intestine found in the post-mortem room may be classified according to infections as follows:

Class I. Pure amoebic dysentery.

    A, proved. Amoebiasis proved by presence of amoebae in

        faeces or tissues, or both .   .   .   .   .   . 39 cases.

                i.e. 64 per cent.

    B, not proved. Amoebiasis diagnosed on morbid anatomical

        grounds only.   .   .   .   . 9 ,,

                i.e. 14 per cent.

Class II. Amoebic plus bacillary dysentery.

    Bacillary type of ulceration (not proved bacteriologically)

        together with proven amoebiasis .   .   .   . 8 ,,

               i.e. 13 per cent.

Class III. Pure bacillary dysentery.

Pure bacillary type of ulceration (not proved bacteriologically :
one case of positive agglutination test for Shiga bacilli)   5 cases.
i. e. 8 per cent.

Post-mortem findings in other tissues than the colon in cases of dysentery.

Before considering the other pathological changes which are associated with dysenteric ulceration of the large intestine, it is necessary to exclude two large groups of cases—

i.e. Cases of dysenteric ulceration accompanied by enteric infections .   9 cases.

Cases of dysenteric ulceration accompanied by gunshot wounds
and complicating diseases other than enteric   .   .   .   22 „

These two groups of cases showed changes in the small intestine, liver, spleen, kidney, &c., such as are found in similar conditions without amoebiasis or bacillary dysentery.

The post-mortem findings in the thirty cases of amoebiasis and dysentery uncomplicated by these conditions are arranged in the table on p. 226.   The terms used are explained in the text.

Small intestine.   In only two cases was the lower part of the small intestine inflamed.   These both occurred in Group A, where amoebiasis was proved by the presence of amoebae in sections of colic ulcers.   In one there was amoebic 'ulcerative colitis' with moderate secondary inflammation.   In the other there were isolated amoebic lesions obscured by secondary diphtheroid inflammation; in this case there was evidence of septicaemia in other organs.   In these two cases the small intestine showed a fibrinous membrane, superficial necrosis of the mucosa, and intense infiltration by neutrophil leucocytes.   There was intense congestion of the rest of the wall and haemorrhage in the submucosa. The dilated veins contained desquamated endothelial cells and neutrophil leucocytes.   There was marked lymphangitis.   The lymphoid nodules and submucous tissues did not contain 'typhoid cells'.   The inflammatory changes were similar to those found in the large intestine around the amoebic lesions.

Colic lymphatic glands.   In all cases the lymphatic glands draining the area of colic ulceration showed slight enlargement.   In cases in which there was extensive ulceration and severe secondary inflammation the glands were as large as small peas.   In no case, however, were the glands as markedly enlarged as in the cases complicated by enteric infection.   In all cases the glands showed a venous congestion which they shared in common with the gut-wall and mesenteric tissues.   In the cases showing severe haemorrhage in the gut-wall there were haemorrhages in the glands.   This condition of the glands I have called, in the table, 'red infiltration'.   It was most conspicuous in cases with the 'bacillary dysenteric' type of colon.

In all cases the sinuses of the lymph glands showed more or less proliferation and desquamation of the sinus cells; these sinus cells were frequently

TABLE V.

Post-mortem Findings in Thirty Cases of Uncomplicated Dysentery and Amoebiasis.

Group A. Cases with Vegetative Entamoebae in the Tissues.

P.M. No.	Dysenteric Lesions in Colon.	Small Intestine.	Colic Lymph Glands.	Liver.	Spleen.	Other Organs.	P.M. Diagnosis.
2	Isolated amoebic ulcers	Nil	Slight inflammation	Slight degeneration	Oedema 6 oz.	Peritonitis : amoebic ulcer perforated	Amoebiasis
7	Amoebic ulcerative colitis	Inflammation of lower 1 foot	Slight inflammation	Slight degeneration	Atrophy 3½ oz.	Slight jaundice	Amoebiasis with inflammation
8	Isolated scarring amoebic ulcers	Nil	Nil	One abscess	Normal 5 oz.		Amoebiasis with liver abscess
11	Amoebic ulcerative colitis	Nil	Red infiltration	Portal infiltration	Slight sepsis 5 oz.		Amoebiasis with inflammation
13	Amoebic ulcerative colitis	Nil	Slight inflammation	Slight degeneration	Atrophy	Acute haemorrhagic nephritis	Amoebiasis
15	Amoebic ulcerative colitis	Nil	Slight inflammation	Two abscesses	Atrophy 4 oz.		Amoebiasis with liver abscess
23	Amoebic ulcerative colitis	Nil	Slight inflammation	Slight degeneration	Normal 5 oz.	Haemorrhage in suprarenal	Amoebiasis with inflammation
34	Bacillary inflammation	Inflammation of lower ileum	Grey infiltration	Portal infiltration	Red septic 7½ oz.		Amoebiasis septicaemia
38	Isolated amoebic ulcers	Nil	Grey infiltration	Portal infiltration	Red septic 15 oz.		Amoebiasis with septicaemia
53	Amoebic ulcerative colitis	Nil	Slight inflammation	Two abscesses	Normal 5 oz.		Amoebiasis with liver abscess

Group B. Cases in which Entamoebae of Pathogenic Type were found in the Faeces during Life but not in the Tissues after Death.

P.M. No.	Dysenteric Lesions in Colon.	Small Intestine.	Colic Lymph Glands.	Liver.	Spleen.	Other Organs.	P.M. Diagnosis.
5	Bacillary inflammation	Nil	Red infiltration	Portal infiltration	Slight sepsis		Amoebiasis with inflammation
6	Isolated amoebic ulcers	Nil	Nil	Atrophy	Atrophy		Amoebiasis
14	Bacillary inflammation	Nil	Red infiltration	Slight degeneration	Normal 5 oz.		Amoebiasis with inflammation

No.		Amoebae					
18	Amoebic ulcerative colitis	Nil	Slight inflammation	Slight degeneration	Normal 5 oz.		Amoebiasis healing
22	Confluent acute amoebic	Nil	Slight inflammation	Slight degeneration	Atrophy 4 oz.		Amoebiasis
24	Bacillary inflammation	Nil	Red infiltration	Hepatitis	Slight sepsis 6 oz.		Amoebiasis with inflammation
26	Amoebic ulcerative colitis	Nil	Slight inflammation	Portal infiltration	Normal 5 oz.	Broncho-pneumonia	Amoebiasis healing
39	Amoebic ulcerative colitis	Nil	Slight inflammation	Slight degeneration	Normal 4 oz.		Amoebiasis with inflammation
48	Isolated amoebic ulcers	Nil	Slight inflammation	Hepatitis	Slight sepsis		Amoebiasis healing
51	Bacillary inflammation	Nil	Slight inflammation	Portal infiltration	Atrophy 3½ oz.	Marked jaundice. Broncho-pneumonia	Amoebiasis with inflammation
54	Isolated amoebic ulcers	Nil	Slight inflammation	Normal	Atrophy	Broncho-pneumonia	Amoebiasis healing

Group C. Cases with no record of Amoebae in Faeces during Life and no Amoebae in Tissues after Death.

No.		Amoebae					
9	Pure bacillary inflammation	Nil	Red infiltration	Slight degeneration	Normal 4 oz.		'Pure bacillary dysentery'
25	Amoebic ulcerative colitis	Nil	Slight inflammation	Portal infiltration	Normal 4 oz.	Haemorrhage in suprarenal. Haemorrhagic infarct of lung.	Amoebiasis
32	Amoebic ulcerative colitis	Nil	Slight inflammation	Slight degeneration	Normal 5½ oz.	Haemorrhagic infarct in lung	Amoebiasis with inflammation
35	Amoebic ulcerative colitis	Nil	Red infiltration	Slight degeneration	Slight sepsis 5½ oz.	Acute haemorrhagic nephritis	Amoebiasis with inflammation
41	Pure bacillary inflammation	Nil	Red infiltration	Portal infiltration	Slight sepsis 5½ oz.		'Pure bacillary dysentery' with septicaemia
44	Pure bacillary inflammation	Nil	Slight inflammation	Hepatitis	Normal 4½ oz.		'Pure bacillary dysentery'
45	Pure bacillary inflammation	Nil	Grey infiltration	Portal infiltration	Slight sepsis 5 oz.		'Pure bacillary dysentery'
55	Isolated scarring amoebic ulcers	Nil	Red infiltration	Hepatitis	Slight sepsis 5 oz.		Amoebiasis healing with inflammation
61	Pure bacillary inflammation	Nil	Grey infiltration	Hepatitis	Grey septic 12 oz.	Lobar pneumonia	'Pure bacillary dysentery' with septicaemia

phagocytic and contained lymphocytes more frequently than neutrophil leuco-cytes. In the cases of red infiltration the sinus cells contained red corpuscles and blood pigment. The other free cells in the sinuses were mainly lymphocytes ; neutrophil leucocytes were relatively few. In four cases the cellular infiltration was sufficiently great to give to the naked eye the appearance of ' grey infiltration '. In three of the four cases in which this change was noted septic spleens indicated the presence of septicaemia. In one of these (Case 61) the colic lesions were of pure bacillary type and the case was diagnosed during life as Shiga bacillary dysentery by agglutination tests ; further, bacillus coli was grown from the blood three days before death (Lieut. Magner). In another (Case 45) the lesions in the colon were also of the pure bacillary type. In the third (Case 34) amoebic lesions were associated with inflammation of the bacillary type. In the fourth (Case 38) amoebiasis was proved by sections, and in addition a motile Gram negative non-lactose fermenter (not identified) was grown from the spleen at post-mortem (Lieut. Magner).

Liver. The commonest change in the liver was cloudy swelling and a little fatty degeneration of the parenchyma cells of the central zone. In nine cases there was in addition a well-marked infiltration of the connective tissues of the portal systems with lymphocytes and plasma cells. In the table I have called this condition ' portal infiltration '. In five other cases there were, in the parenchymatous tissues, necroses, infiltrated with a few neutrophil leucocytes, and also a cellular infiltration of the portal systems associated with proliferation of connective tissue cells. This condition I have called ' hepatitis '.

' Portal infiltration ' and ' hepatitis ' occurred not only in cases with amoebic lesions but also in cases with the pure bacillary dysentery type of colon. One example of hepatitis (Case 48) may have been a Weil's disease complicating convalescence.

Amoebic abscess of the liver was present in three cases. In one there was a single abscess in the liver and two small granulating ulcers, without amoebae, in the caecum. In the other two cases there were two abscesses in the liver and numerous amoebic ulcers in the colon ; the caecum was chiefly affected in one case, the sigmoid in the other. One of these cases is worthy of fuller record :

Case No. 53. Had an indefinite illness with occasional attacks of slight diarrhoea. Pain in appendix region. Appendicitis diagnosed and appendix removed. No diarrhoea in hospital until a week later, when severe intestinal haemorrhage, followed by death in twenty-four hours. Faeces almost pure blood with some flakes of mucus containing vegetative entamoebae.

Post-mortem. Large sloughing, nearly perforated, amoebic ulcers in caecum and ascending colon ; scattered ' bouton de chemise ' ulcers in hepatic flexure and sigmoid colon. Two large amoebic abscesses in right lobe of liver ; rupture of one of these on under surface, giving rise to a well-localized subhepatic and subdiaphragmatic abscess.

In all three cases the abscesses were situated in the right lobe, were of large size, and contained typical gelatinous débris enclosed by a ragged wall. In one case the pus was markedly haemorrhagic.

Microscopically. Vegetative entamoebae were readily demonstrated in scrapings from the walls of the abscesses ; the débris contained no recognizable liver cells. The sections showed, at the edge of the abscess, a granular eosinophilous débris containing pyknotic nuclear fragments and neutrophil leucocytes. In the more central débris there was complete chromatolysis. Vegetative entamoebae were numerous in the débris close to the abscess wall. The wall of the abscess was formed by a broad zone of granulation tissue in which the liver cells were isolated or destroyed and in which there was some haemorrhage. The granulation tissue showed a marked infiltration with lymphocytes, plasma cells, and relatively few neutrophil leucocytes ; there was also proliferation of connective tissue cells and capillary endothelial cells. Vegetative entamoebae were present in the granulation tissue, especially in capillary blood-vessels, but were not numerous. The infiltration by lymphocytes and plasma cells was especially marked in the connective tissues of the portal systems, and spread in these tissues for a considerable distance from the wall of the abscess. In all cases there were thrombi in the large branches of the portal vein, and the thrombi contained vegetative entamoebae ; some of the veins showed necrosis of their walls. In all cases there was haemorrhage in the central zones of the liver lobules at a distance from the abscess wall. In one case a thrombus in the hepatic vein projected into the inferior vena cava.

Spleen. In sixteen cases the spleen was normal or atrophic. In eight cases, although not much enlarged, it showed slight inflammatory changes. In three cases the spleen showed marked septic enlargement. In two of these amoebiasis was proved by the presence of amoebae in the intestinal lesions. The amoebic lesions in one (Case 38) were complicated by severe inflammation, and a motile Gram negative bacillus was isolated from the spleen at post-mortem ; in the other the amoebic lesions were obscured by a diphtheroid inflammation (bacillary dysentery type). In the third (Case 61) there were no amoebic lesions, the case being one of the five which resembled pure bacillary dysentery ; a positive agglutination to Shiga bacilli was obtained during life in this case. These three cases belong to the group of four in which the colic lymphatic glands showed ' grey infiltration '.

Kidney. In only two cases were there severe lesions in the kidney. In these there were glomerular haemorrhages, and severe degeneration of epithelium in the first convoluted tubules and ascending loops of Henle : that is, acute haemorrhagic nephritis was present. In both of these cases amoebic ulcerative colitis was associated with severe inflammation in the colon. In the remaining cases there was a slight degree of cloudy swelling in the first convoluted tubules and ascending loops of Henle, and, in some cases, a slight fatty degeneration of the epithelial cells of the collecting and discharging tubules.

Suprarenal. In two cases there was haemorrhage in the cortex and medulla of one suprarenal, with ' marantic thrombosis ' of the central vein.

Peritoneum. On opening the abdomen in all cases of dysenteric ulceration of the colon, dilatation of the subserous and mesenteric veins of the colon was

conspicuous. This venous dilatation involved the larger veins, especially the inferior mesenteric veins and, in some cases, the portal vein.   Blood-films obtained by puncture of the subserous veins showed, in one case, vegetative entamoebae, refractile cells, endothelial cells, and neutrophil leucocytes, and in three cases refractile cells, endothelial cells, and neutrophil leucocytes.   Curious tangle clots (not ordinary post-mortem clots) were obtained from the portal vein in two cases.   These thrombi contained many endothelial cells.   Owing to lack of time, investigation of blood-films from the veins was only occasionally possible.

Urinary bladder.   In none of these thirty cases was there any change in the urinary bladder.   It may be mentioned here, however, that in three of the cases of dysenteric ulceration complicated by other infections (Sections 2 and 3, pp. 231, 233) I found lesions about the trigone of the bladder.   In two cases there was subepithelial haemorrhage and diphtheroid inflammation on the surface.   In one case there was scarred ulceration about the trigone.   I did not find amoebae in the tissues.   Cystitis was a common complication of dysentery, and I found vegetative entamoebae in three specimens of urine sent from the wards.

Lungs.   In three cases there was a terminal broncho-pneumonia.   In one case there was a terminal lobar pneumonia.   In two other cases there were single haemorrhagic and necrotic foci in the lungs ; these lesions were apparently embolic ; amoebae were not found therein.

Heart.   The heart frequently showed atrophy.   There were occasionally minor degrees of fatty degeneration in the muscle fibres.

An analysis of the changes in the above organs brings out a point of value for the differentiation of enteric and dysenteric cases in the post-mortem room. In the dysenteric cases inflammatory enlargement of the regional lymphatic glands was never so great as in cases of enterica.   The enlargement was greatest (grey infiltration) in two (45 and 61) of the cases of 'pure bacillary dysentery', in one case (34) of amoebic lesions complicated by inflammation of the bacillary type, and in a case (38) of amoebiasis from the spleen of which motile Gram negative bacilli were cultivated.   The only septic spleens which could be compared with those of enterica were found in three of these cases (61, 34, and 38). It may therefore be concluded : first, that the regional glands and spleen in dysentery do not show inflammatory changes comparable to those of enterica unless there is septicaemia following bacterial inflammation of the intestine ; secondly, that such a septicaemia may result from a bacterial inflammation complicating amoebic dysentery, but it is more likely to occur in those cases with extensive submucous haemorrhage and widespread superficial necrosis in the colon (' pure bacillary dysentery ').

The causes of death in dysenteric ulceration.

Of these 61 cases 37 died from amoebiasis or the direct results of dysenteric ulceration.

Exhaustion . . . . 17 cases.
Septicaemia of intestinal origin (not enteric) . . 4 „
Haemorrhage from dysenteric ulcers . . . 7 „

(In many of these cases which died from exhaustion haemorrhage was an important factor in causing exhaustion.)

Terminal pneumonia . . . . . . 4 cases.
Perforated amoebic ulcers . . . . . 3 „

(In other cases ulcers were perforated, but the perforations were closed by adhesions.)

Amoebic abscess of liver . . . . . 2 cases.

(In the other case of liver abscess death was due to a sudden intestinal haemorrhage.)

These causes of death illustrate the important complications of amoebic dysentery.

Haemorrhage was by far the most important complication with which the clinicians had to deal.

Perforations were frequently cured naturally, as evidenced by post-mortem findings as well as by clinical observations.

Liver abscess was difficult to diagnose in the frequent presence of hepatitis, which subsided readily under the emetine treatment. It had been missed in two out of the three cases which came to the post-mortem room.

Pneumonia was relatively uncommon in dysenterics though extremely common in enterics.

Septicaemias of intestinal origin were probably far more common than is indicated by the above number in ' causes of death '.

Section 2.   Cases (9) of Dysenteric Ulceration associated with Enteric.

Group A.   Cases with vegetative entamoebae in tissues.

P. M. No. 1.   Clinically enteric; no clinical dysentery.   Typical enteric ulcers in small intestine.   Medullary infiltration of mesenteric lymph glands. Septic spleen (10 oz.).   Amoebiasis confined to sigmoid colon.   Typical amoebic ulcers.

P. M. No. 30.   Clinically enteric and amoebic dysentery.   Paratyphoid B by blood culture (Lieut. Davies), amoebae in faeces (Capt. J. G. Thomson and G. B. Bartlett), medullary infiltration of lymphoid follicles and enteric ulcers in lower 6 feet of small intestine.   Severely inflamed mesenteric lymph glands. Septic spleen.   Confluent amoebic ulcers of ulcerative colitis type throughout colon.

P. M. No. 46.   Had enteric and, when convalescent, developed dysentery. Amoebae persisted in faeces in spite of treatment.   Had dysentery for three months.   Healed enteric ulcers in lower 6 feet of small intestine.   Amoebiasis throughout colon and a great number of amoebae in sections.   Inflammation of bacillary type throughout colon.

Group B. Cases in which entamoebae of pathogenic type were found in faeces during life but not in tissues after death.

P. M. No. 4. Clinically enteric and amoebic dysentery. A lengthy illness. Temperature came down and dysentery improved, but diarrhoea persisted. Healed enteric ulcers in lower 3 feet of ileum. Typical isolated amoebic ulcers complicated by severe inflammatory changes. Amoebic ulceration most marked in sigmoid.

P. M. No. 20. Clinically enteric. Paratyphoid B by agglutination (G. B. B.). During convalescence developed dysentery. Healing enteric ulcers in lower 12 feet of small intestine. Enlarged mesenteric glands and spleen (7 oz.). Amoebiasis throughout colon most marked in descending colon. Much membranous inflammation of the ' bacillary dysenteric ' type.

P. M. No. 33. Ill seven weeks; not inoculated. Clinically enteric ; paratyphoid B by agglutination (G. B. B.). Did well and then developed dysentery. Amoebae present in faeces (Capt. J. G. Thomson). No change in small intestine. Typical amoebic ulcers in caecum ; confluent ulceration in rest of colon ; ulcerative colitis type. Marked grey infiltration of colic lymph glands. Septic spleen (10 oz.).

P. M. No. 40. Had enteric, and when convalescent developed dysentery. Healing enteric ulcers in lower 5 feet of the small intestine. Typical amoebic ulcers throughout colon. Marked enlargement of colic lymph glands.

P. M. No. 56. Admitted for dysentery. Amoebae present (Capt. J. G. Thomson and G. B. B.). Then developed pyrexia of enteric type ; paratyphoid B by blood culture (Lieut. Davies). Medullary infiltration in Peyer's patches of lower 9 feet of ileum. Typical isolated and confluent amoebic ulcers throughout the colon. Septic spleen. Medullary infiltration of mesenteric and colic lymph glands.

Group C. Cases with no record of amoebae in faeces during life and no amoebae in tissues after death.

P. M. No. 49. Clinically enteric with perforation. Operation : laparotomy and drainage. Paratyphoid B by agglutination (Lieut. Davies). No ulceration of small intestine. Isolated ulcers of amoebic type and much confluent ulceration (ulcerative colitis type) in large intestine. Post-mortem putrefaction severe : doubtful amoebae found in sections. Paratyphoid B isolated from spleen and gall-bladder by Lieut. Davies.

These nine cases exemplify the difficulties of diagnosis which faced the clinicians and pathologists who were dealing with the Gallipoli epidemics ; dysenteric and enteric epidemics occurring coincidently, it was inevitable that there should be double infections with protozoa and bacilli of the enterica group. From a consideration of these nine cases it appears that paratyphoid B and amoebic dysentery was a common combination. Thus in two cases paratyphoid B bacilli were isolated by blood culture during life (Lieut. Davies). In three other cases the diagnosis was made by agglutination tests, and in one of these was confirmed by post-mortem cultures (Lieut. Davies). In two of these cases in which there was infection by paratyphoid B, namely one case diagnosed by agglutination tests during life and one case diagnosed by agglutination during life and culture after death, no lesions were present in the small intestine and amoebic ulcers alone appeared to be present in the large intestine. In the other

four cases the clinical diagnosis of enteric was borne out by finding typical lesions in the small intestine, glands, and spleen, but no laboratory tests were done to identify the member of the enteric group responsible for the lesions. This conclusion that paratyphoid B and amoebic dysentery was a common combination coincides with that based on the results of agglutination tests on dysenterics by myself and others in the early stages of the epidemics.

The solution of the question as to whether the cases were enteric complicated by amoebiasis or amoebiasis complicated by enteric is very difficult. Clinically, enteric preceded dysentery in six of the cases. In two cases the diseases appeared to be coincident. In one case (56) the dysentery definitely preceded the enteric. A consideration however of the other post-mortem results, especially those in Group A, shows that amoebic ulcers were frequently present without clinical dysentery. It is therefore possible that amoebic ulcers were present in the six cases before they developed enteric. The two cases in which no lesions were present in the small intestine, and no enteric lesions could be recognized in the large intestine, give strong support to the view that enteric bacilli can gain access to the body via amoebic ulcers in the colon.

Examination of the results of post-mortem investigation of *all* the dysenteric cases shows that involvement of the small intestine generally indicated an infection by enteric bacilli (seven cases) rather than other organisms, presumably dysenteric bacilli (two cases). In this connexion it is well to remember that paratyphoid B ulceration of the small intestine may not have the typical appearance of typhoid ulceration. The intestinal lesions in cases of amoebiasis associated with paratyphoid infection had been considered by some observers to be lesions of bacillary dysentery. This mistake was corrected by reference to Lieut. Davies's blood cultures and by the demonstration of medullary infiltration in the Peyer's patches of the small intestine with typical enteric lesions in lymphatic glands and spleen at post-mortem.

Section 3.   *Cases* (22) *of Dysenteric Ulceration associated with Gunshot Wounds or Diseases other than Enteric.*

Group A.   Cases with vegetative entamoebae in tissues.   13 cases.

P. M. No. 3.   Admitted for gunshot wound of chest.   Had had 'peninsular diarrhoea'.   Developed signs of peritonitis, but chest condition overshadowed abdominal condition.

Acute widespread amoebic ulceration in caecum and ascending colon. Numerous isolated lesions in rest of colon. Perforation of caecum. Haemothorax from bullet wound.

P. M. No. 10.   Admitted for gunshot wound of chest.   Did not have clinical dysentery.   Died from empyema and broncho-pneumonia in consequence of the wound.   Septic spleen.   Very widespread early acute discrete amoebic ulceration in colon; confluent ulceration in caecum.

P. M. No 12.   Admitted for gunshot wound of abdomen.   Died of general peritonitis, after drainage of abdomen.   No clinical dysentery.   A few isolated amoebic ulcers in descending colon and rectum.

P. M. No. 16. Admitted for gunshot wound of head. Did well, but died suddenly from angina pectoris. At post-mortem there was a thrombus on an atheromatous button blocking the left coronary artery at its bifurcation. A few isolated amoebic ulcers in caecum and sigmoid colon.

P. M. No. 17. Admitted for gunshot wound of chest with empyema. Developed dysentery about a week before death. Died from empyema. Isolated ulcers containing amoebae, and severe inflammation of the bacillary type throughout colon and rectum.

P. M. No. 27. Admitted for gunshot wound of head. Developed slight dysentery shortly before death; amoebae in stools. Died from internal pyocephalus and basal meningitis in consequence of the wound. A few rounded and confluent amoebic ulcers in descending colon and rectum.

P. M. No. 29. Admitted with hepatic insufficiency. Died from bronchopneumonia and cirrhosis of liver of hobnail type. Five large transverse amoebic ulcers and a few 'bouton de chemise' ulcers in sigmoid.

P. M. No. 31. Had no diarrhoea and no pyrexia. Comatose and smelt of acetone. Died from broncho-pneumonia and diabetes. Rounded and transverse amoebic ulcers in sigmoid colon.

P. M. No. 42. Gunshot wound of buttock and femur eleven days before death. Streptococcal septicaemia. Had had 'peninsular diarrhoea'. In hospital had colic, but was constipated. Died of septicaemia. Large grey septic spleen. Isolated amoebic ulcers of various sizes throughout colon; some confluent in caecum and ascending colon.

P. M. No. 43. Had gall-bladder removed for suppuration five weeks before death. Operation wound broke down. Clinical dysentery four days before death. Died from peritonitis around operation wound. Typical amoebic ulceration; in parts severe confluent in descending colon; perforated ulcer closed by adhesions.

P. M. No. 50. Gunshot wound of foot twelve days before death. Streptococci in blood culture. Had no clinical dysentery. Died from pyaemia; abscesses in lungs, &c. Sparsely scattered nodules, 'bouton de chemise' ulcers and transverse ulcers in caecum and ascending colon. Some ulcers through to peritoneum and nearly perforated.

P. M. No. 52. Admitted for gunshot wound of chest with empyema and septicaemia. No clinical dysentery. Died from septicaemia and empyema. A few 'bouton de chemise' ulcers in caecum; two large transverse ulcers in ascending colon; group of scarring ulcers in sigmoid colon.

P. M. No. 58. Admitted for gunshot wound of legs; gangrene and sepsis. Developed dysentery one day before death. Amoebae found in faeces by Capt. J. G. Thomson. Died from septicaemia with gangrene of leg, &c. Two minute amoebic ulcers in caecum; marked congestion of mucosa in sigmoid and rectum.

Group B. Cases in which amoebae of pathogenic type were found in the faeces during life but not in the tissues after death. 5 cases.

P. M. No. 19. Admitted for gunshot wound of spine; cord not involved. Developed septicaemia, and also dysentery; amoebae in stools. Dysentery lasted three weeks and amoebae were still present fourteen days after treatment commenced. Died from septicaemia. Septic spleen. Isolated rounded and transverse ulcers throughout colon; much secondary inflammation in descending colon.

P. M. No. 21. Admitted for gunshot wound of neck. Developed broncho-pneumonia. Had dysentery four weeks before death; amoebae in stools. Treated and cured. Died from broncho-pneumonia with gangrene of lung. Scarred amoebic ulcers in caecum and descending colon; those in sigmoid large and transverse, almost encircling the lumen of the gut.

P. M. No. 28. Admitted for lobar pneumonia. Then developed dysentery. Amoebae in stools. Grey hepatization of lung. Rounded and confluent amoebic ulcers throughout colon and upper rectum, 'ulcerative colitis' type.

P. M. No. 37. Admitted for gunshot wound of femur. Developed dysentery three weeks before death; amoebae in stools. Appendicostomy performed at a very late stage of the disease. Septic gunshot wound, but died of the dysentery. Isolated amoebic ulcers in caecum and ascending colon; confluent ulceration, ulcerative colitis type, in the rest of the colon and rectum, almost perforated in the sigmoid colon.

P. M. No. 60. Admitted two months before death with appendix abscess. Abscess drained. Developed dysentery; amoebae in stools. Dysentery cured. Developed empyema secondary to peritonitis. Died from intestinal obstruction due to peritoneal adhesions. A few healed and healing amoebic ulcers in sigmoid and rectum; one scar in caecum.

Group C. Cases with no record of amoebae in faeces during life and no amoebae in tissues after death. 4 cases.

P. M. No. 36. Admitted for lobar pneumonia. No dysentery whilst in hospital. Died with grey hepatization of whole right lung. Group of rounded and transverse granulating ulcers in sigmoid colon.

P. M. No. 47. Admitted for septic gunshot wound of thigh with fractured femur. In hospital about 120 days altogether; had two attacks of dysentery; apparently cured by emetine treatment. Died from septic wound. Scarred transverse ulcers in sigmoid colon; much submucous fibrosis in sigmoid and rectum.

P. M. No. 57. Admitted for subacute meningitis. No clinical dysentery. Died from hydrocephalus and subacute cerebrospinal meningitis. A few isolated rounded and transverse granulating ulcers in lower colon and rectum.

P. M. No. 59. Admitted for frost-bite. Feet amputated, but legs became gangrenous. No clinical dysentery. Died from broncho-pneumonia and abscess of the lung. A few small rounded granulating ulcers in the caecum.

An analysis of these twenty-two cases shows that none were admitted to the hospital for dysentery; moreover, eleven of the cases had no clinical dysentery whilst in hospital. If accurate histories had been obtained it would doubtless have been found, as it was in two of the cases, that the patients had had peninsular diarrhoea. Whether there was, or was not, previous diarrhoea, the eleven cases demonstrate the presence of extensive ulceration in the absence of clinical dysentery during the patients' stay in hospital. The absence of clinical dysentery in the presence of extensive amoebic lesions in the upper part of the colon is well illustrated by post-mortems Nos. 10, 42, 50, and 52.

The frequency of these cases where the amoebic ulcers were found 'by accident' in the post-mortem room induced us to conclude *as a working rule*: that when a patient developed clinical dysentery the ulceration was far more

extensive than the duration of the history would lead one to suppose; in fact, we concluded that amoebiasis was an extremely insidious disease and was frequently not accompanied by clinical dysentery. There were in this group notable exceptions to our working rule, e. g. Case 51, in which there was a marked clinical dysentery and only two minute ulcers in the caecum.

In eighteen of these twenty-two cases amoebiasis was proved either by sections (thirteen cases) or by faecal examinations (five cases). Inasmuch, therefore, as the patients were admitted to the hospital for causes other than dysentery, we concluded that amoebiasis was extremely common amongst the troops on the peninsula, far more common than any statistics of clinical dysentery could indicate.

It is, of course, possible that in some of the cases amoebiasis was contracted within the hospital. Thus a few cases occurred amongst the staff of the hospital. The majority, however, of the cases died within a few days of admission ; considering, therefore, the extent of the lesions and allowing for an incubation period, they could not have contracted the disease after admission. I investigated this question with some care and, basing my opinion on the extent of the lesions and an incubation period of fourteen days, came to the conclusion that very nearly all the cases were infected on the peninsula. In all four cases of Group C the ulcers were granulating or healed. It is possible that three of these—Cases 36, 57, and 59—represent a natural cure of amoebiasis. They may, however, have been treated and cured on the peninsula; accurate histories of previous treatment were not obtainable. That natural cure of amoebic ulceration of the intestine is possible, is proved by one of the cases of liver abscess; here two small granulating ulcers in the caecum were the sole amoebic lesions in the colon.

PART VI. THE EFFECT OF TREATMENT ON AMOEBIASIS.

The routine treatment of all cases of dysentery was that recommended by Sir Ronald Ross. This treatment has already been described in discussing the effect of treatment on the cytological content of the stools (p. 207). It may be summarized as : injections of emetine hydrochloride, administration of saline purgatives and bismuth mixture, rest in bed, and careful diet.

The effects of this treatment, as gauged by an examination of the faeces and the associated clinical signs and symptoms in thirty selected cases, have already been discussed. In the great majority of the cases the amoebae and 'refractile cells' disappeared in about six days ; the stool remained purulent for a variable time after the disappearance of the protozoa. In a few cases a thorough course of treatment failed to eliminate the amoebae and refractile cells.

Analysis of the cases in the post-mortem room confirms and amplifies these findings. The success of the treatment in eliminating amoebiasis is well illustrated

by Group B, Section 1 (p. 218). In this group, when compared with Group A, the routine treatment had been on the average much more thorough, amoebae were not found in the tissues, and in five out of the twenty-one cases the amoebic lesions were healing or healed. The occasional failure of the treatment is illustrated by some of the cases in Group A. In one case the treatment had been as thorough as in any of Group B, but numerous amoebae were present in all the ulcers examined. In three other cases in which between five and ten grains of emetine had been administered numerous amoebae were found in the ulcers. Group B further explains the persistence of purulent diarrhoea after the disappearance of amoebae from the stools. In this group the relative preponderance of cases showing the severer forms of secondary bacterial inflammation is conspicuous. In thirteen cases such severe inflammation of the ulcerated colon was present, and was the cause of death. In these a purulent diarrhoea persisted until death.

It is clear, therefore, that treatment in amoebic dysentery must be designed, not only to remove amoebiasis, but to combat secondary infection. Emetine injections alone are not sufficient. The administration of saline purgatives and bismuth mixture in the routine treatment proved of service in combating secondary infection. The importance of bismuth salts has been proved in the Panama epidemics of amoebic dysentery; cases were very successfully treated by the administration of bismuth salts alone.

Polyvalent antidysenteric serum prepared in Alexandria from local strains of dysenteric bacilli was said to be useful in those cases where a purulent diarrhoea persisted in spite of the cure of amoebiasis by emetine treatment. This was a potent serum; it agglutinated all my strains of dysenteric bacilli as well as paratyphoid A and B. I do not know how it was prepared. The Lister antiserum was said to be much less efficacious.

Opinions as to the value of antiserum treatment varied greatly; the majority of the clinicians placed no reliance on it.

PART VII. GENERAL CONCLUSIONS.

1. The epidemic of dysentery among the troops upon the Gallipoli peninsula was due to amoebic infection.

In the examination of 477 stools which had the appearance of dysenteric stools, vegetative amoebae of pathogenic type were found in 379, or 79·4 per cent.

At the post-mortem examination of 61 cases of dysenteric ulceration of the intestine, amoebic lesions were found in 56, or 91·8 per cent.

2. Amoebic infection was more prevalent on the peninsula than the symptoms and signs in the hospital indicated.

In the routine examination of 652 stools which had not the appearance of

dysenteric stools, vegetative amoebae of pathogenic type were found in 118, or 18 per cent.

In 11 of the 56 cases in which amoebic lesions were found at post-mortem examination there had been no signs or symptoms of dysentery whilst the patients were in hospital. Comparisons of the lesions with the length of stay in hospital showed that infection contracted in hospital was excluded in almost all these cases.

3. An indication of the prevalence of amoebic infection in the troops is given by the results of the total number of routine examinations of faeces and post-mortem examinations.

Between June, 1915, and February, 1916, 1,129 specimens of faeces were examined; vegetative entamoebae of pathogenic type were found in 497, or 44 per cent.

During the same period, 142 complete post-mortem examinations of the body were made; the head was not always examined. Amoebic lesions were found in 56, or 39·4 per cent.

4. The epidemic of amoebic dysentery was accompanied by an epidemic of enterica.

5. Lesions of enterica were found in 41 of the 142 complete post-mortems, or 28·8 per cent.

6. Amoebic dysentery associated with enterica infection was relatively common.

In the 56 cases in which amoebic lesions were found on post-mortem examination enterica infection occurred in 9, or 16 per cent.

7. In the 9 cases in which both amoebic dysentery and enterica infection were present, acute or healed enteric lesions, together with amoebic ulcers, were found in the intestine in 7 ; amoebic ulcers alone were found in 2. In the latter 2 cases infection by paratyphoid B was demonstrated by agglutination before death and also in 1 case by culture after death. The condition of the glands and spleen was such as is found in enterica infection.

8. Amoebic lesions in the intestine were very frequently associated with a secondary bacterial infection of varying intensity. This secondary infection led, in some cases, to a septicaemia of intestinal origin.

9. In some cases this secondary infection was very intense, so that the amoebic lesions were obscured by a diphtheroid inflammation resembling that found in bacillary dysentery.

10. In 5 cases an inflammation of this kind was present alone, no amoebic lesions being detected.

11. Inasmuch as amoebic ulceration may be complicated not only by enteric but by secondary bacterial infections it is essential that, for the complete elucidation of any case of dysentery, all possible methods of investigation should be employed. The examination of faeces and post-mortem material for amoebae must be supplemented by bacteriological and serological investigation.

12. On the other hand, the employment of bacteriological and serological methods alone will give an entirely erroneous idea of the initial infection in amoebic dysentery. Examination of faeces for amoebae and post-mortem examination cannot be dispensed with in the investigation of dysentery.

13. The bacteriological and serological investigations in the series of cases examined post-mortem were, unfortunately, very incomplete. They give no indication of the number of cases in which secondary inflammation in intestines showing amoebic lesions was caused by bacilli of the dysenteric group. When the complicating infection was intense and resembled that seen in bacillary dysentery it has been tentatively diagnosed as 'bacillary dysentery'. In only one of the five cases in which amoebic lesions were absent and an inflammation of this type was present was there evidence of a specific infection by organisms of the dysenterica group. These 5 cases have been tentatively called 'pure bacillary dysentery'.

14. Allowing the tentative diagnosis mentioned in the preceding paragraph, the 61 cases of dysenteric ulceration examined in the post-mortem room may be classified according to infections as follows :

(a) Pure amoebic ulceration . . . . 41 cases, or 67 per cent.
(b) Amoebic ulceration and enterica infection 7 cases, or 11·4 „
(c) Amoebic ulceration plus enterica infection
    plus dysenterica infection . . . 2 cases, or 3 „
(d) Amoebic ulceration plus dysenterica in-
    fection . . . . . . 6 cases, or 9·8 „
(e) Pure dysenterica infection . . . 5 cases, or 8 „

15. The routine treatment (injection of emetine hydrochloride, administration of saline purgatives and bismuth mixture, with rest in bed and careful diet), recommended by Sir R. Ross, was successful in curing amoebiasis in the majority of the cases ; in some cases a thorough administration of the treatment failed to eliminate amoebiasis.

16. In some cases treated in this way, although vegetative amoebae disappeared from the stools, a purulent diarrhoea persisted.

17. This persistent diarrhoea was due to the persistence of secondary bacterial inflammation. Thus a special group of cases was found post-mortem in which the treatment applied in the wards had been on the average most thorough and in which after death no amoebae were found in the tissues. Many of the amoebic lesions were healing or healed, but secondary bacterial inflammation was specially pronounced.

18. It is, therefore, most important that specific treatment should be administered early so that the amoebic ulceration may be arrested before it has rendered the colon more vulnerable to secondary bacterial invasion.

19. It is further important that the routine treatment in amoebic dysentery should be designed not only to eliminate amoebiasis but to combat bacterial infection of the intestines. The saline purgatives and bismuth mixture in the

treatment adopted proved of service in this respect. If an antiserum is employed it should be polyvalent.

20. In addition to secondary bacterial inflammation of the intestines the most serious complications of amoebic dysentery were: Intestinal haemorrhage, intestinal perforation, septicaemia of intestinal origin, amoebic abscess of liver (5·3 per cent.), and broncho-pneumonia. Of these, haemorrhage was the most frequent.

21. Amoebic ulceration may be present in patients who present no signs or symptoms of dysentery.

22. In the examination of stools for protozoa, and in particular for vegetative entamoebae, microscopic examination of unstained material should be supplemented by examination of films fixed when wet and subsequently stained.

23. In the faeces and in the tissues vegetative entamoebae are frequently associated with 'refractile cells'.

24. The 'refractile cells' represent a stage in the life cycle of the pathogenic entamoeba. Their presence is, therefore, of diagnostic value.

25. The appearance of the colon when infected by pathogenic entamoebae varies greatly both in different areas in individual cases and in different cases.

26. This variation depends upon the intensity of the amoebic infection, the stage of the infection, and the degree to which the amoebic lesions are complicated by bacterial infection. In certain cases the amoebic lesions are obscured by such secondary inflammation and can only be revealed by section of the gut.

27. In lesions of certain types, particularly the smaller lesions, amoebae are much more likely to be found.

28. In order, therefore, to ensure the detection of amoebic infection in the post-mortem room the colon must be examined with great care, small ulcers and foci of diphtheroid inflammation should be incised, and a number of the smaller lesions should be selected for microscopic examination.

29. In order to determine the presence of vegetative entamoebae and refractile cells in post-mortem material, microscopic examination of scrapings from ulcers and of blood-films from the dilated subserous veins is a valuable supplement to the examination of sections of embedded material; it enables a large number of lesions to be examined rapidly.

30. Such scrapings and blood-films should be examined, as in the case of faeces, both in unstained films and in films fixed when wet and subsequently stained.

DESCRIPTION OF FIGURES.

PLATE 26. *Faecal Cytology.* Films and slides stained with Weigert's iron-haematoxylin and counterstained with van Gieson's stain.
$\frac{1}{12}$ Zeiss oil immersion. No. 4 Zeiss eyepiece. Zeiss drawing apparatus. Drawing-board at level of microscope-stand on bench.

FIGS. 1–9. *Vegetative entamoeba histolytica or tetragena in the pathogenic entamoeba.*

FIG. 1. A large entamoeba showing a spongy cytoplasm and small condensations of chromatin on the nuclear membrane.
P. M. film from Case No. 53.

FIG. 2. A large entamoeba showing crescentic condensations of chromatin on the rim of the nucleus.
Faecal film from a non-fatal case.

FIG. 3. An entamoeba showing a moderate degree of vacuolation in the cytoplasm.
Faecal film from a non-fatal case.

FIG. 4. A large entamoeba fixed whilst moving, showing marked vacuolation of its cytoplasm.
P. M. Section from Case No. 46.

FIGS. 5 and 6. Smaller entamoebae showing typical nuclei with crescentic arrangement of chromatin on the nuclear membrane and an ill-defined nodule of chromatin in the centre of the nucleus.
P. M. Section from Case No. 53.

FIG. 7. A very small entamoeba with a small cytoplasmic pseudopodium. A typical ring nucleus with a small nodule of chromatin in the middle of the nucleus.
Faecal film from a non-fatal case.

FIG. 8. An entamoeba containing a nodule of chromatin which resembles the nucleus of a body-cell. The nucleus of the amoeba shows crescentic arrangement of chromatin on its rim.
P. M. Section from Case No. 46.

FIG. 9. An entamoeba showing a large vacuole in its cytoplasm and a second vacuole containing a nodule of chromatin. The nucleus of the amoeba shows the typical ring appearance.
Faecal film from a non-fatal case.

PLATE 27. *Faecal Cytology.* Films stained with Weigert's iron-haematoxylin and counterstained with van Gieson's stain.
$\frac{1}{12}$ Zeiss oil immersion. No. 4 Zeiss eyepiece. Zeiss drawing apparatus. Drawing-board at level of microscope-stand on bench.

FIGS. 10–17. *'Refractile Cells.'*

FIG. 10. 'Refractile cell' showing three condensations of chromatin on the margin of its delicate nuclear membrane. Cf. nuclei of the vegetative entamoebae (Figs. 2 and 8).
Faecal film made during life. P. M. No. 28.

FIG. 11. 'Refractile cell' showing two fusiform masses of chromatin on its nuclear membrane. If the fine nuclear membrane was badly stained these two fusiform masses of chromatin would resemble 'chromidia'.
Faecal film from a non-fatal case.

FIG. 12. 'Refractile cell' showing an excentric nucleus with chromatin in nodules on the nuclear membrane. Cf. nucleus of the vegetative entamoeba (Fig. 1).
Faecal film from a non-fatal case.

FIG. 13. 'Refractile cell' with a greatly swollen nucleus which appears to be extruded from the cytoplasm of the cell.
Faecal film from a non-fatal case.

FIG. 14. 'Refractile cell' with one large and one small nucleus.
Faecal film made during life. P. M. No. 28.

FIG. 15. 'Refractile cell' with two large and one small nucleus.
Faecal film made during life. P. M. No. 28.

FIG. 16. 'Refractile cell' with two large and one small nucleus. In this and in Fig. 15 there were two small nuclei, but they were superimposed: for the sake of clearness one of them is excluded from the drawing. The nuclei show the typical crescentic arrangement of chromatin. The small nucleus closely resembles that of a vegetative entamoeba.
    Faecal film from a non-fatal case.

FIG. 17. 'Refractile cell' in which the outlines of two large and four small ring nuclei are indicated.
    Faecal film from a non-fatal case.

FIG. 18. Clump of large endothelial cells from a blood-vessel. The cells show typical large endothelial cell nuclei which are undergoing chromatolysis. One large cell shows a refractile cell nucleus with fusiform collections of chromatin on the nuclear membrane.
    Faecal film from a non-fatal case.

PLATE 28. *Faecal Cytology.* Films and slides stained by Weigert's iron-haematoxylin and van Gieson.
    $\frac{1}{12}$ Zeiss oil immersion. No. 4 Zeiss eyepiece. Zeiss drawing apparatus. Drawing-board at level of microscope-stand on bench.

FIGS. 19–28. *Inflammatory Cells, &c.*

FIG. 19. A large endothelial cell from a lymph sinus. The cytoplasm is swollen and vacuolated. The nucleus shows a typical fine network of chromatin.
    Film from scraping of P. M. No. 53.

FIG. 20. A phagocytic endothelial cell, macrophage, showing the typical nucleus of an endothelial cell. In the vacuoles in its cytoplasm are a lymphocyte and a neutrophil leucocyte.
    Faecal film from a non-fatal case.

FIG. 21. A macrophage containing a lymphocyte.
    Section from P. M. No. 53.

FIG. 22. A macrophage with a greatly swollen degenerating nucleus. In its cytoplasm are three ingested chromatin masses.
    Faecal film from a non-fatal case.

FIG. 23. A macrophage, the nucleus of which has degenerated: the two chromatin masses in its cytoplasm possibly represent the remains of its nucleus. It contains an ingested neutrophil leucocyte.
    Faecal film from a non-fatal case.

FIG. 24. A macrophage with an obscured nucleus: it contains four lymphocytes and the remnant of another cell.
    Section from P. M. No. 53.

FIG. 25. Two columnar epithelial cells from the mucous membrane of the colon: one shows a vacuolated protoplasm (with mucicarmine stain the mucus in these vacuoles would be red).

FIG. 26. Two plasma cells: note the small nuclei with abundant nodules of chromatin.
    (The cytoplasm would stain red with Unna Pappenheim's stain.)

FIG. 27. Neutrophil leucocyte.

FIG. 28. Red blood corpuscle.

PLATE 29. *To show the staining reactions of the vegetative entamoeba.*
    $\frac{1}{6}$ Zeiss. No. 4 Zeiss eyepiece. Zeiss drawing apparatus. Drawing-board at level of microscope-stand on bench.

FIG. 1. Vegetative entamoeba in a blood-vessel of the submucosa of the colon. Stained by Weigert's iron-haematoxylin and counterstained by van Gieson's stain. The cytoplasm of the vegetative entamoebae is slate grey and their nuclei show distinctly. Red blood corpuscles and the protoplasm of muscle-cells are stained yellow. Coliagenous fibres of the adventitia of the vessel are stained bright red.

FIG. 2. Vegetative entamoebae in a blood-vessel. Stained by Twort's mixture of light green and neutral red. The cytoplasm of the vegetative entamoebae takes the red 'nuclear' stain. The nuclei of the entamoebae are not obvious with this stain.

FIG. 3. Vegetative entamoebae in a blood-vessel. Stained by Jenner's stain. The cytoplasm of the vegetative entamoeba takes the 'nuclear' stain.

Figs. 1, 2, and 3 are from sections of colon in Case No. 38.

FIG. 4. Vegetative entamoebae in submucous tissues around a blood-vessel. Stained by Ehrlich's acid haematoxylin and counterstained by eosin. The cytoplasm of the vegetative entamoebae is markedly haematoxyphil and is vacuolated : the ring nuclei show very distinctly : they do not resemble the nuclei of any of the body cells. The vegetative entamoebae vary considerably in size. There is no cellular infiltration in the tissues around them.

Fig. 4 is from a section of colon in Case No. 53.

PLATE 30. *Section across a typical 'bouton de chemise' ulcer.* (See letter A in Plate 6.)

Section from Case No. 50 stained by Ehrlich's acid haematoxylin and eosin.

Zeiss A₂ lens. No. 2 Zeiss eyepiece. Zeiss drawing apparatus. Drawing-board at level of microscope stand.

The section does not include the whole of the raised nodule. Much of the necrotic debris has come away from the ulcer. The ulcer is undermined, i. e. the necrosis has involved the submucosa beneath the edges of the ulcer and the mucosa with its muscularis mucosae overhangs. The ulcer is deep, nearly reaching the muscle coat. The submucosa is very wide ; the submucosa shows, under a higher power, serous exudation and haemorrhage with amoebae in the tissues. There is a well-marked cellular infiltration in the submucosa. The blood-vessels in the submucosa are engorged. There are a number of greatly dilated veins in the mesenteric fat. Many of the veins were thrombosed.

PLATE 31. *Portions of colon showing thickset acute amoebic ulcers and confluent acute amoebic ulceration.* (Type (*a*) ulceration in the text.)

The upper drawing is of a portion of descending colon, and the lower drawing a portion of ascending colon. Both from Case No. 3.

The upper drawing shows numerous small ulcers ; these show as pits with a raised margin. The letter A is placed beneath a typical 'bouton de chemise' ulcer. By the confluence of these small lesions an ulcer of the type above the letter B is produced. The whole of this ulcer stands out from the level of the mucous membrane of the gut, and in the ulcer is ragged yellow debris which frequently has a pitted or honeycombed appearance. Some of the ulcers tend to spread transversely. Vegetative entamoebae were readily found in all these ulcers.

The lower drawing shows a late stage : the end product in these cases with thickset amoebic lesions. The mucous membrane between the confluent ulcers has sloughed ; the surface has a ragged villous appearance and there is nothing resembling ordinary mucous membrane. In sections of this necrotic mass it is generally impossible to demonstrate vegetative entamoebae.

PLATE 32. *Right hand. Portion of colon showing an isolated group of amoebic ulcers.* (Type (*b*) ulceration in the text.)

Left hand. Portion of colon showing confluent amoebic ulcers of the 'ulcerative colitis' type. (Type (*c*) ulceration in the text.)

The right-hand drawing is from the descending colon to Case No. 15. The left-hand drawing is from the descending colon of Case No. 23.

The right-hand drawing shows that the mucous membrane of the colon, apart from the group of amoebic lesions, is intact. The group of ulcers is prominent ; it appears to stand up from the level of the mucous membrane. The ulcers contain the typical yellow necrotic débris which indicates that amoebae are present. There is a small slit-shaped ulcer on the summit of one of the rugae.

The left-hand drawing shows deep ulcers alternating with bands and islands of mucous membrane. The general direction of the ulcers is transverse and the appearance is precisely similar to that commonly seen in ulcerative colitis of the sporadic type met with in England. The small amoebic ulcers have run together ; the débris has escaped and deep ulcers reaching the muscle coat alternate with inflamed remnants of mucosa and submucosa. Vegetative entamoebae were not found in these advanced lesions, but they were present in the smaller lesions in this intestine.

PLATE 33. *Portion of colon showing confluent amoebic ulceration.* (Type (*c*) ulceration in the text.)
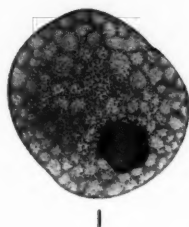
This drawing is of a portion of descending colon in Case No. 13.

The drawing shows deep, clean-based ulcers alternating with islands and bridges of mucous membrane. Tags of mucous membrane are left hanging into the lumen of the gut. There is a great deal of undermining of the mucous membrane, and a bristle has been passed beneath one bridge of mucous membrane. The general direction of the ulcers is transverse, and the muscle coat can be seen in the bases of the ulcers. This appearance is commonly seen in ulcerative colitis of the sporadic type in England. Amoebae were not found in these advanced lesions, but they were present in the smaller lesions of this intestine.
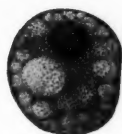
PLATE 34.   *Portion of colon showing 'pure bacillary' dysenteric lesions.*

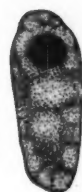This drawing is of a portion of ascending colon in Case No. 44.

The drawing shows extreme congestion of the mucous membrane with patches of green diphtheroid membrane on the surface.   There is a shallow serpiginous ulceration involving the superficial part of the mucous membrane; but there is none of that deep undermining of the mucous membrane which has been illustrated in amoebic lesions.   There might, however, be deep ulceration obscured by the patches of diphtheroid membrane.   Such deep ulcers containing amoebae were found in some intestines of this type.   (Type (*d*) in text.)   In this case amoebic ulcers were not found, and it is classed as a 'pure bacillary dysentery'.
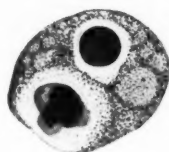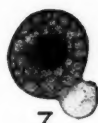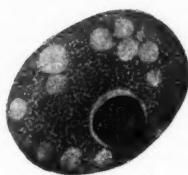
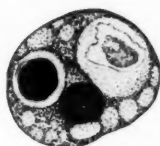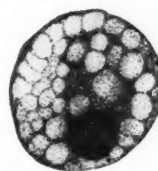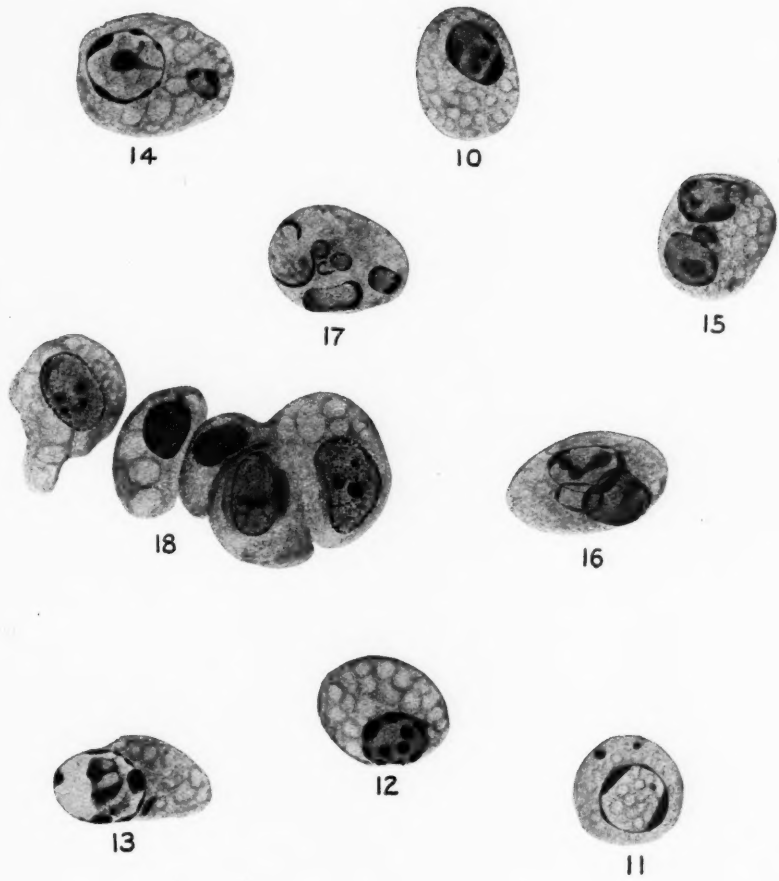J.R. FORD del.

14 10 17 15 18 16 13 12 11

J.R.FORD DEL.

1

2

3

4

J.R.FORD del.

J.R. FORD DEL.

Mucosa

Submucosa

Muscular coat

Mesenteric fat
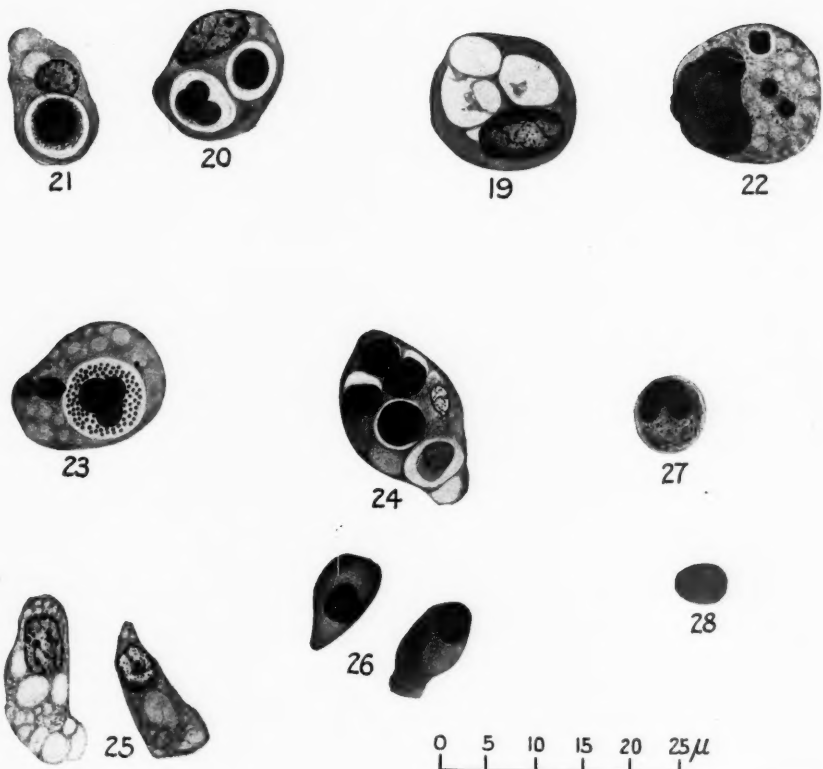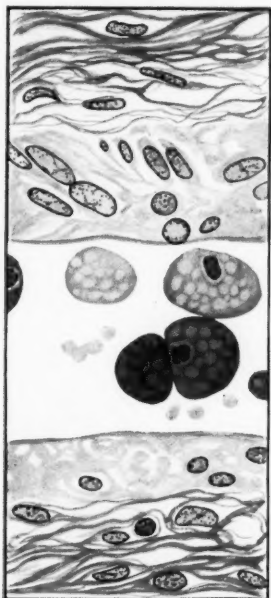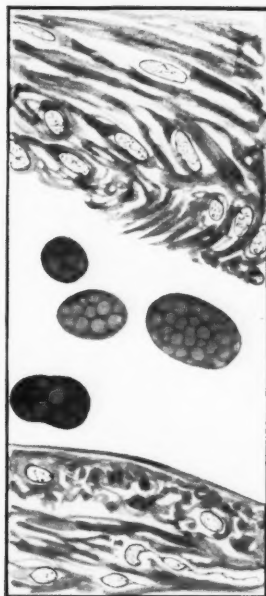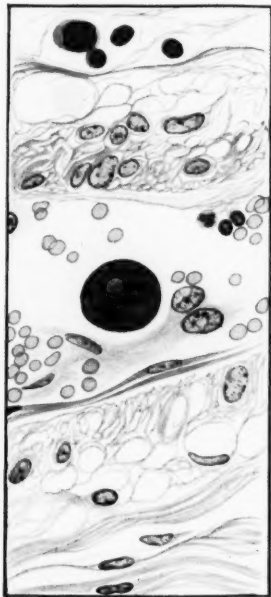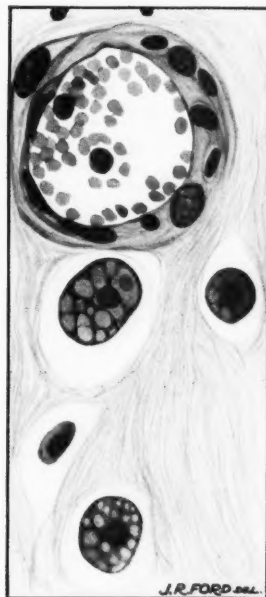
W.T.SHIELLS

W.T.SHIELLS

W.T.SHIELLS

DIABETES INNOCENS

By GEORGE GRAHAM

(From the Pathological and Chemical Laboratories, St. Bartholomew's Hospital)

DIABETES mellitus is usually considered to be a serious disease, and the prognosis is in most cases a grave one. However, it is well established that the glycosuria which occurs in elderly people, the so-called alimentary glycosuria, has a very different significance from that which occurs in young adults and children, for in the latter the discovery of glycosuria is thought to be of very evil import. But this is not always the case, as a fair number of cases have now been recorded which run a very different course to that of true diabetes mellitus.

The first case of this kind was recorded by Klemperer (1) in 1896. The amount of sugar which was excreted was very small and the man showed no other signs or symptoms of diabetes mellitus. As the man also excreted albumin, the name of renal diabetes was given to the condition. Lüthje (2) and Bönniger (3) described cases in which glycosuria and albuminuria were present. Lüthje pointed out that the amount of sugar excreted in the urine bore no relation at all to the amount of sugar eaten and that the amount of sugar in the blood was less than normal.

These cases all showed signs of disease of the kidneys, but another group of cases has been described in which no discoverable lesion of the kidney existed.
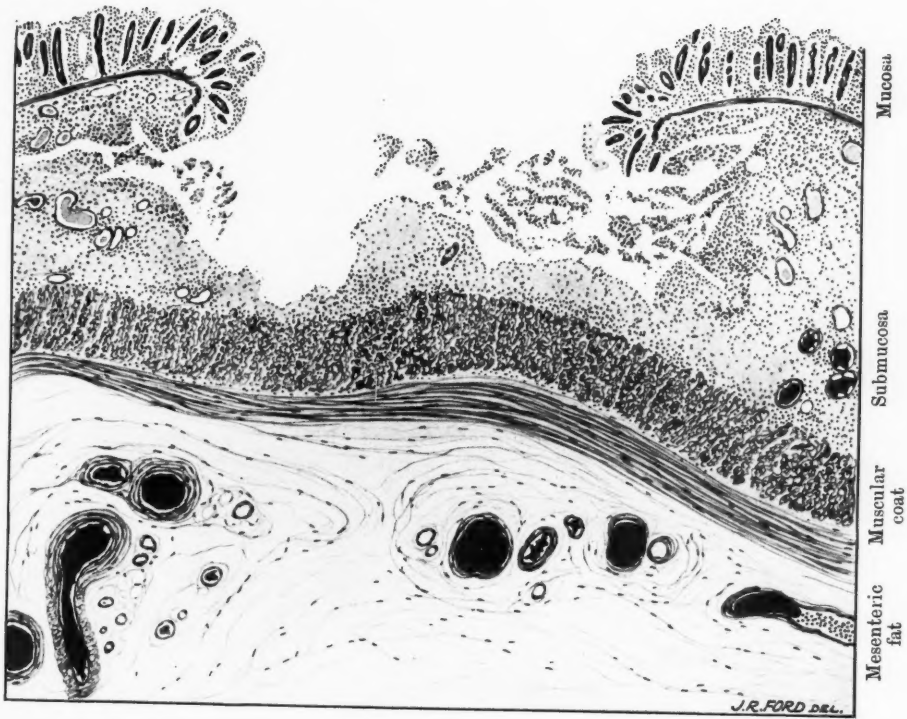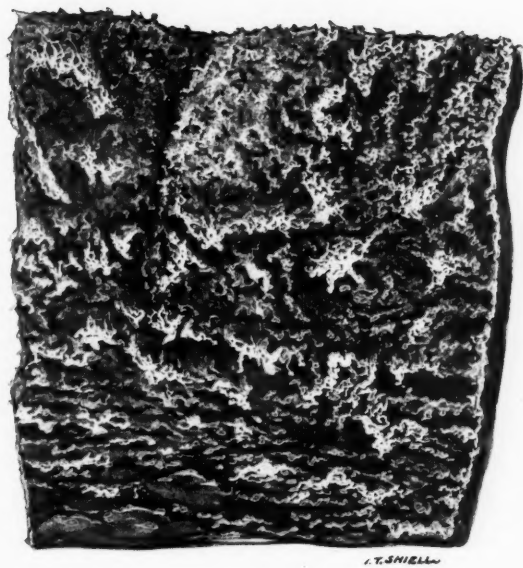
Thus Weiland (4) described three cases of this kind in 1907, and Garrod (5) recorded one case in 1912. Salomon (6) collected nine cases which belong to this group and suggested the name of diabetes innocens. Riesman (7) has also described three similar cases.

The ages of these patients varied from 6 to 30 or 40, and in most cases it is probable that the sugar had been excreted for many years, as its presence was only discovered by accident. The amount of the sugar was very small, less than 10 grm. a day, and bore very little relation to the amount of sugar eaten, as a dose of 100 grm. of sugar caused an excretion of only 2–10 grm. of sugar. In these cases the amount of sugar in the blood lay within the normal limits. There were no symptoms which could be ascribed to the presence of the glycosuria and the condition remained stationary. These cases seem to form a definite clinical entity and bear no relation to the true diabetes mellitus.

But there are other cases which, although they resemble the diabetes

innocens cases in many ways, do not belong to quite the same class. Thus, in 1914, Garrod (8) recorded the case of a girl of 7 years (Case IV of this series) who excreted 20–30 grm. of sugar : the concentration in the urine was often 4 per cent. The occurrence of a glycosuria of this concentration in a young girl of 7 years would usually be regarded as evidence that she had diabetes mellitus, but the course which the case has run almost certainly negatives that diagnosis.

Working in conjunction with Dr. Garrod I have examined two other cases of this kind, and Parkes Weber (9) has described one case, and the case recorded by Lewis and Mosenthal (10) seems to resemble these cases.

These cases also differ from the diabetes innocens class in that the amount of sugar excreted in the urine is not quite independent of the amount of sugar eaten. They resemble the diabetes innocens class in that the level of the blood sugar before a meal lies within the normal limits. But they differ from the innocens cases described by Salomon in that the level of the blood sugar is altered by a dose of sugar. Salomon found that the level of the blood sugar was not affected by a dose of 100 grm. of sugar, but he did not state how soon after the dose of sugar the estimation of the blood sugar was made.

The effect of a dose of sugar on the level of the blood sugar in healthy adults has recently been investigated by A. Th. B. Jacobson (11), Bing and B. Jakobsen (12), and Graham (13). Their results have shown that the level of the blood sugar rises very soon after a dose of 100 grm. of sugar, and the change may be apparent within ten minutes. The greatest amount of sugar in the blood is often found after twenty minutes, but the rise is very transient, as the blood sugar usually falls to its former level about one hour after the dose of sugar, though it may be raised for another hour.

This work throws quite a new light on carbohydrate metabolism, and an investigation was therefore undertaken to study the behaviour of the diabetes innocens cases and to see whether their carbohydrate metabolism was in any way deranged. Five cases have been examined, two of which belong to the diabetes innocens class of Salomon, while the other three belong to a new group. The estimations of the blood sugar were all made by Bang's method, into which certain slight modifications were introduced (13).

Case I. T. A well-developed man, aged about 30. No other member of the family passes sugar and there was no consanguinity in his parents. The sugar was first detected in February, 1914. At that time he felt nervous, suffered from coldness of hands and feet, and had fainted once. There was neither thirst nor polyuria. During the next year he ate a fairly strict diet, but sugar was always excreted in small amounts and the percentage varied from 0·5 to 0·85 per cent. In January, 1915, he began to eat carbohydrates again, but avoided sugar. In July, 1915, he was tested with a dose of sugar (Fig. 1). The urine from 6 p.m. on July 14 to 9 a.m. on July 15 contained 0·4 per cent. of sugar which was shown to be dextrose by the osazone tests. On July 15 the urine passed between 4 and 4.30 p.m., four hours after the last meal, contained only a trace of sugar. The level of the blood sugar at 4.35 p.m. was 0·105 grm. per cent., and forty minutes later, after 50 grm. of sugar, was 0·14 grm.

per cent. During the three hours after the meal 200 c.c. of urine were excreted, containing 1·2 per cent. of sugar and 2·4 grm. in all. Thus out of 50 grm. of sugar eaten 2·4 grm., or 5 per cent., were excreted by the kidney.
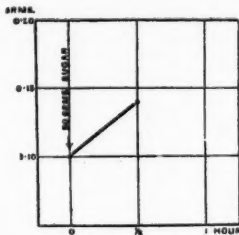

FIG. 1.

Case II. L. F. Captain R.A.M.C. A well-developed man, aged 28. No history of consanguinity on either side of the family, but two other members pass sugar.

(*a*) A sister. Sugar was first detected when she was 23 years old. She was strictly dieted for three years, but the sugar was always present in the urine. During this time she felt unwell and lost two stone in weight. The diet was then relaxed, and she has kept well for the last twelve years. During that period she has married and has borne children without causing any symptoms referable to the glycosuria. No details are available as to the amount of sugar excreted, or whether it is still being excreted.

(*b*) A brother. Sugar was discovered during an examination for life insurance in 1907, at the age of 24, and a year later sugar was still present. He has never dieted himself and is alive and well, but no details are available about the amount of sugar excreted or whether it is still being excreted.

L. F. tested his own urine when he was 20 years old (1908) and discovered the presence of the sugar. He was seen by Dr. Pavy, who told him that he had 'a family idiosyncrasy involving a slight defect of carbohydrate assimilative power' and stated that he had seen similar cases. It seems clear from this that Dr. Pavy was acquainted with this class of case, but I am not aware of his having written anything on this subject. L. F. has never worried about the glycosuria and has been well except for two periods. In 1912 he went to Egypt, but soon came home as he felt very limp and was losing weight rapidly. His weight decreased by 17 lb. and during the last few weeks by 1 lb. each week.

He went to Scotland, ate an ordinary diet with plenty of honey, and regained 12 lb. of weight in four weeks. At that time he was seen by Dr. Garrod and the percentage of sugar was 0·44 per cent. During the next two years he remained well and joined the R.A.M.C. in October, 1914. In August, 1915, he became limp and unwell, although his work in France was neither very dangerous nor very arduous. He came home on sick leave in September, 1915, and the percentage of sugar excreted was 0·47. After two months' leave he felt well and energetic again.

Although L. F. has never dieted himself for long periods, he states that the sugar disappears when a strict diet is eaten and is usually absent from the night urine. On January 6, 1916, his sugar tolerance was tested with a dose of sugar. A meal containing no carbohydrates was eaten at 12 noon: the urine passed between 1 p.m. and 3 p.m. contained 0·9 grm. of sugar, which gives an hourly rate of excretion of 0·45 grm. (Figs. 2 and 3). The level of the blood sugar at 3 p.m. was 0·12 grm. per cent., and thirty minutes after a dose of 37 grm. of sugar had risen to 0·14 grm. per cent.; after one hour it was still at 0·135 grm.

per cent., but after two hours it had fallen to 0·125 grm. per cent. During the
first hour after the dose of sugar, 2·4 grm. of sugar were excreted, and the
'extra' sugar was about 2 grm. In the second hour the sugar output was
0·9 grm. and the 'extra' sugar about 0·5 grm. In the next forty minutes
0·57 grm. of sugar was excreted, which gives an estimated output of 0·85 grm.
for the third hour. Thus of 37 grm. of sugar eaten only 2·8 grm. of 'extra'
sugar were excreted.

In this case both the family and the personal history show that the disease
is certainly of a very innocent character. Both Cases I and II are clearly very
similar to the nine cases described by Salomon. They differ slightly in that the
blood sugar does rise slightly after the dose of sugar, but the rise is no greater
than that which occurs in normal individuals.

In these cases it is clear that the sugar is constantly excreted, although the
blood sugar lies within normal limits.

The next three cases differ in certain important respects from the pre-
ceding ones.
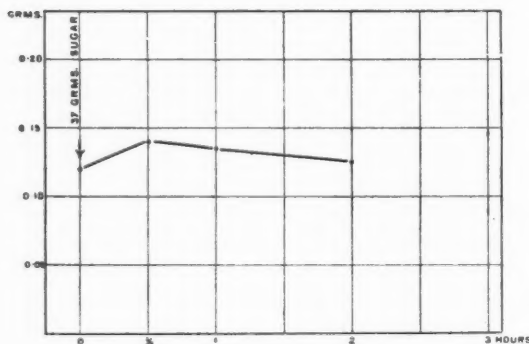
Fig. 2.
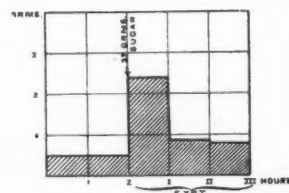
Fig. 3.

Case III (14). D. W. Temp. Major R.A.M.C. A well-developed man,
aged 33. No history of consanguinity in the family. His father, a doctor,
occasionally passes sugar but never diets himself. In 1911 sugar was discovered
in the urine during the routine examination for a life insurance. D. W. thinks
that his urine had been tested once before whilst a student, but he is not
quite certain of this. During the first few months after the discovery of the
glycosuria he ate a strict carbohydrate-free diet, and the figures for two weeks
are shown in Table I.

The total sugar excreted varied from 24 to 56 grm. and the percentage from
1·6 grm. per cent. to 4·0 grm. per cent. A temporary relaxation of the diet did not
cause any subsequent rise in the sugar output. During the last five years he has
eaten an ordinary diet, but has abstained from eating sweet things. He has
kept well, except for two illnesses, and has shown no other symptoms of diabetes
mellitus. In 1911 he had some enlarged glands in the neck which were thought
to be tuberculous. In 1914 he had an attack of abdominal pain which after
careful investigation was ascribed to the presence of enlarged and probably
calcified tuberculous glands.

Although it was recognized that he was not a true diabetic, it was not until
1915 that the relation between his blood sugar and sugar metabolism was
worked out. In March, 1915, the fasting value of his blood sugar was 0·12 grm.
per cent., and the total sugar output on an ordinary diet was 40 grm. The
fasting level of the blood sugar was not altered when the Von Noorden vegetable-

egg diet was eaten, for it remained at 0·13 grm. per cent. to 0·14 grm. per cent., although the total sugar output in the urine fell to 5 grm. After the second vegetable-egg day only a trace of sugar could be detected, but no alteration occurred in the level of the blood sugar.

TABLE I.

A diet containing very little carbohydrate was eaten.

1911.	Total Sugar per 24 hours in grm.	% of Sugar.	Vol. c.c.	Specific gravity.
Jan. 30	55	4·0	1380	1030
„ 31	21	2·0	1050	1025
Feb. 1	56	3·6	1550	1030
„ 2	44	2·7	1630	1027
„ 3	46	3·6	1280	1028
„ 4 ⎫ „ 5 ⎭	Diet relaxed completely			
„ 6	32	2·0	1600	1018
„ 7	30	2·0	1500	1022
„ 8	37·5	2·5	1500	1026
„ 9	24	1·6	1500	1028
„ 10	37·5	2·5	1500	1025
„ 11	37·5	3·3	1140	1028
„ 12	48	3·0	1600	1029
„ 13	25	2·2	1140	1029
„ 14	28	2·0	1400	1027

FIG. 4.

Hence there is in this case some relation between the amount of sugar excreted and that eaten, but it is also clear that sugar is excreted even when the blood sugar is within the normal limits.

The effect of definite amounts of sugar on the level of the blood sugar and on the sugar output was then investigated.

(a) On May 28, 1915, a dose of 60 grm. of sugar was given in the form of oatmeal and bread (Figs. 4 and 5).

The fasting value of the blood sugar was 0·9 grm. per cent., which was rather lower than the figure obtained three months earlier. Thirty minutes after the meal it had risen to 0·15 grm. per cent.; after seventy-five minutes it had fallen to 0·11 grm. per cent., after three hours to 0·09 grm. per cent., and after four hours to 0·075 grm. per cent. (The rise in this case was rather less than that which occurred in the case of G. G. (Fig. 4, dotted line), which was taken

when he was fatigued, although in his case no sugar was excreted) (13). The total sugar excreted during 8½ hours of the night was 3·0 grm., and the hourly rate of excretion was 0·37 grm. The meal was not eaten until three-quarters of an hour after the night urine had been passed, but during this period and in the
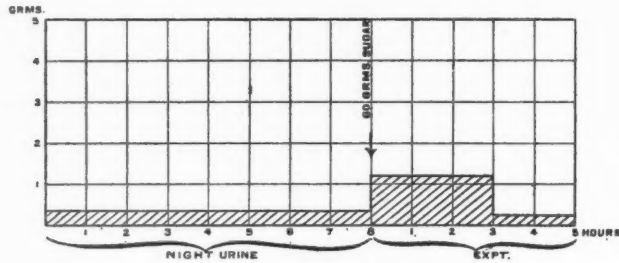
Fig. 5.
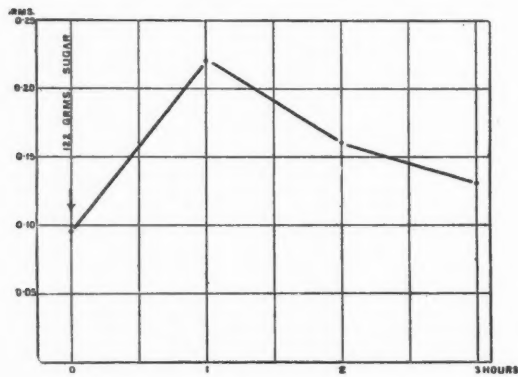
Fig. 6.
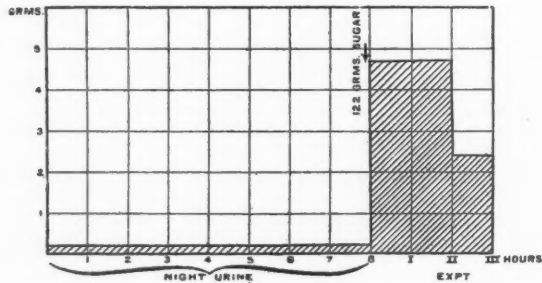
Fig. 7.

2½ hours after the meal 3·75 grm. of sugar were excreted at an hourly rate of 1·2 grm. In the next two hours 0·5 grm. was excreted and the hourly rate was 0·25 grm. Therefore after an intake of 60 grm. of sugar 4·25 grm. of sugar were excreted, and the 'extra' sugar was 2·75 grm., or 4·6 per cent. of the sugar eaten.

(b) On June 25, 1915, a dose of 100 grm. of sugar and 44 grm. of bread, = 122 grm. of sugar, was given fasting (Figs. 6 and 7).

The level of the blood sugar before the meal was 0·095 grm. per cent., and one hour later it had risen to 0·22 grm. per cent.: after two hours it had fallen to 0·16 grm. per cent., and after three hours to 0·13 grm. per cent. The rate of excretion during the night was 0·2 grm. per hour, and during the first two hours after the meal 9·4 grm. of sugar were excreted, or 4·7 grm. per hour. In the third hour, while the level of the blood sugar was falling from 0·16 grm. per cent. to 0·13 grm. per cent., 2·4 grm. of sugar were excreted. Thus out of a dose of 122 grm. of sugar 11·9 grm. were excreted in three hours, and the 'extra' sugar was 11·3 grm., or 10 per cent. of the total intake. The level of the blood sugar was considerably higher than that which occurs in a healthy adult after that amount of sugar.

The significance of these figures will be discussed with those of the next two cases.
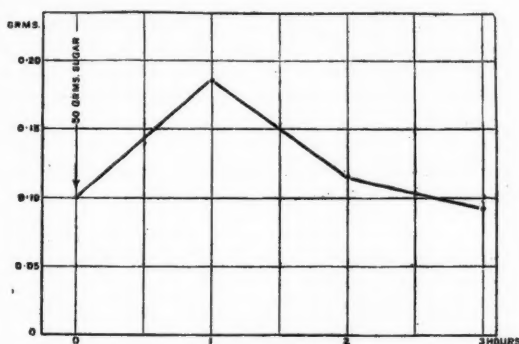
FIG. 8.
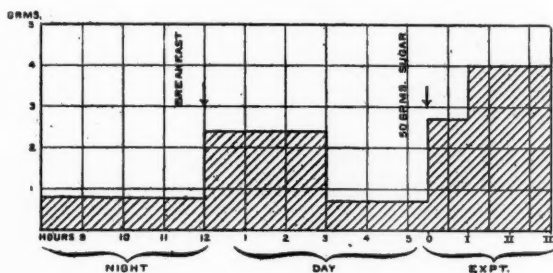
FIG. 9.

Case IV. Alice H., aged 12.
Case V. Herbert H., aged 14.

The father's parents were first cousins, and one of the father's cousins passed sugar at the age of 22, four years ago, but is now alive and well.

Alice H. was seen by Dr. Garrod (8) in 1911 at the age of 8. She then complained of nocturnal enuresis and diurnal frequency. The total sugar excreted varied between 20 to 40 grm. a day. The sugar output was not decreased by a carbohydrate-free diet, although a considerable increase in the acetone bodies occurred and she was very drowsy. Since 1911 she has eaten an ordinary mixed diet, but does not eat sugar. In 1913 she was apparently quite

well and still passed the same amounts of sugar. Sugar tests with 10, 20, and 50 grm. of glucose were carried out by R. L. M. Wallis. With the small amounts no relation between the dose of sugar and the amount of sugar excreted could be detected, but after 50 grm. of sugar the hourly rate of excretion rose from 0.85 grm. per hour to 2·6 grm. per hour for two hours. The blood sugar was also estimated by R. L. M. Wallis by his own method and the blood was found to contain 0·06 grm. per cent. of sugar on one occasion. The excretory power of the kidney for sodium chloride and potassium chloride was tested by Schlayer's method (G. G.) and was practically normal. In 1915 she was keeping well and was quite up to the average in stature and intelligence, although she was rather a thin child. The blood sugar was 0·12 grm. per cent. and 0·14 grm. per cent. on two occasions some hours after a meal, although the sugar excreted on one occasion contained 4·5 per cent. of sugar. In June, 1915, she was tested with a dose of 50 grm. of sugar five hours after a meal (Figs. 8 and 9). The level of the blood sugar before the sugar was eaten was 0·10 grm. per cent., and one hour later it was 0·185 grm. per cent.: after two hours it had fallen to 0·13 grm. per cent., and after three hours to 0·09 grm. per cent. The hourly rate of the sugar excretion during the night was 0·8 grm. and rose to 2·4 grm. for three hours after a meal of toast and eggs. In the 2½ hours before the experiment began 0·7 grm. of sugar per hour was excreted. In the second and third hours, although the level of the blood sugar had fallen, 4 grm. of sugar were excreted each hour. The experiment was stopped at this point owing to the necessity of giving her another meal. During the three hours after the meal 10·7 grm. of sugar and 8·3 grm. of 'extra' sugar were excreted out of a dose of 50 grm. of sugar, that is, 17·2 per cent. of the intake.

Case V. Herbert H., aged 15, elder brother of Alice H. Sugar was discovered at the age of 13 in 1913 in the course of a routine examination of the urine of the whole family. He was then a well-developed boy who showed no symptoms of disease. The sugar output was little altered as the effect of gradually reducing the carbohydrates (Table II).

<center>TABLE II.</center>

						Sugar output.
Protein and fat diet + 168 grm. of sugar as bread .	.	.	.	.	39–42 grm.
„ „ + 112 „ „ .	.	.	.	.	33–20 „
„ „ + 56 „ „ .	.	.	.	.	34–23 „
Vegetable and egg day .	.	.	.	.	.	20 „

The concentration of the sugar in the urine was 5·7 per cent. on admission, but after a while it fell to 2·0 per cent.

Since 1913 he has eaten an ordinary diet, although he often eats sweets. He has kept very well, and now, aged 15, he is working long hours in Woolwich Arsenal.

In March, 1915, his blood sugar was 0·14 grm. per cent. some hours after a meal, although the urine passed contained 4 per cent. of sugar. In August, 1915, he was tested with a dose of 80 grm. of sugar (Figs. 10 and 11). The level of the blood sugar was 0·11 grm. per cent. and 0·115 grm. per cent. at 6 and 7 a.m., and thirty minutes after the dose of sugar it had risen to 0·225 grm. per cent.: after one hour it had fallen to 0·15 grm. per cent., and after two hours it was still at that level. The estimations of the sugar for the third hour were spoilt, but four hours after the dose of sugar the level of the blood sugar had fallen to 0·12 grm. per cent. The night urine was collected in two portions, and the hourly rate from 8 p.m. to 2 a.m. was 1·4 grm., while that from 2 a.m. to 6.50 a.m. was 2·1 grm. This may be due to the fact that he was unable to pass urine at 6 a.m. and during the next fifty minutes was endeavouring to do so in order that the experiment might start, and he was somewhat distressed over the

difficulty. In the first hour after the dose of sugar 3·7 grm. of sugar were excreted; in the second hour, 4·0 grm.; in the third and fourth hours, 1·5 and 1·2 grm. of sugar were excreted. Thus the total of sugar excreted in four hours was 12·6 grm., and assuming that the usual hourly rate was 1·4 grm., the 'extra' sugar was 7·0 grm. out of an intake of 80 grm., or 8·7 per cent. of the intake.
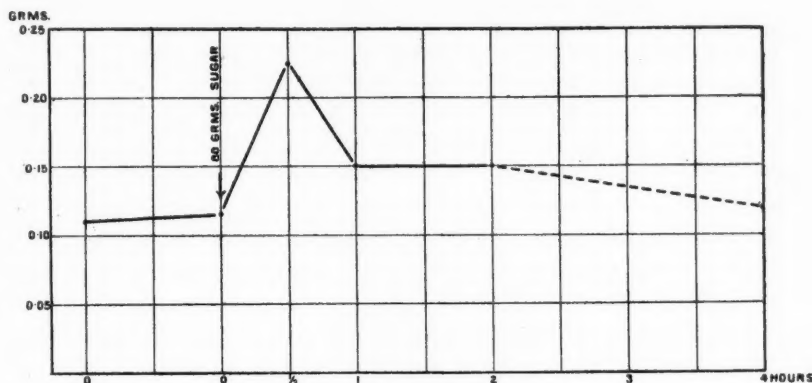
Fig. 10.
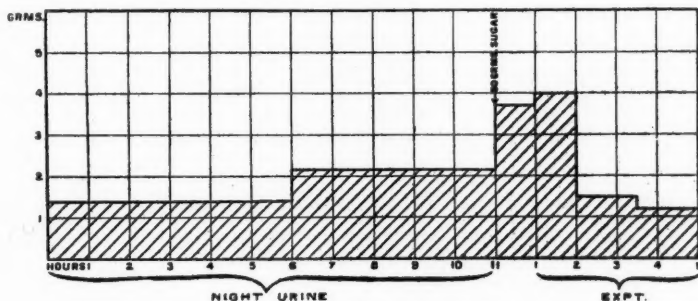
Fig. 11.

Discussion.

The examination of these cases shows that they bear no relation to the case of renal diabetes described by Klemperer, for none of them showed any sign of renal disease. But it is clear that Cases III, IV, and V are not quite analogous with Cases I and II of this series, or with those described by Salomon, for the amount of sugar excreted is much greater, e. g. 20–50 grm. instead of less than 10 grm. Again, the percentage of sugar in the urine may be as much as 5 per cent., whereas in Salomon's case it is usually less than 1 per cent. The effect of a dose of sugar was also greater, as from 7 to 17 per cent. of the sugar was excreted instead of 1 to 2 per cent. Lastly, the level of the blood sugar was rather higher than that of a normal individual after a dose of sugar.

A comparison of Cases III, IV, and V shows that A. H. and H. H. are very similar, but that D. W. is rather different in some points. However, they seem to form a definite clinical group, and it is possible that other cases may be found which will form a connecting link with the other type.

The mechanism by which the sugar escapes through the kidney into the urine is not easy to understand, and at least two hypotheses are possible :

1. That the sugar is passively excreted through the renal epithelium.

2. That the sugar is actively excreted by the renal epithelium.

The association of the definite disease of the kidney in Klemperer's case suggested that just as albumin escaped so sugar also escaped, and that there was a definite 'leakage'. Again, in the diabetes innocens case, the small amount of sugar excreted, and the fact that the amount of sugar was not affected by the extra dose of sugar, suggested that a definite 'leakage' of sugar was taking place. In the new class it also seemed probable, at first sight, that a leakage was taking place. For it would presumably be much easier for sugar to escape when the level of the blood sugar is raised after a meal. The experiments of D. W. suggested that this was the case, as the rise in the sugar output took place after the meal. But in his case it was difficult to obtain hourly specimens of urine, and the urine was collected in three-hourly periods. It was possible to collect the urine from A. H. and H. H. in hourly periods, and the results are very interesting. Thus A. H. excreted 2·8 grm. of sugar during the first hour, when the blood sugar was rising from 0·10 grm. per cent. to 0·18 grm. per cent., and 4·1 grm. in the second hour, though during that hour the blood sugar fell from 0·18 grm. per cent. to 0·13 grm. per cent., and in the third hour 4·0 grm., although the level of the blood sugar at the beginning of the hour was 0·13 grm. per cent. and 0·11 grm. at the end of it.

It is of course possible that the blood sugar may have been raised between the times that the blood was tested, but the experiments on G. G. (13), which were done at more frequent intervals, do not suggest that this is at all likely. The experiment on H. H. shows this more clearly. The level of the blood sugar rose from 0·11 grm. per cent. to 0·22 grm. per cent. after thirty minutes and fell to 0·15 grm. per cent. after sixty minutes. During the period 3·8 grm. of sugar were excreted. At the end of the second hour the level of the blood sugar was 0·14 grm. per cent. and 4·0 grm. of sugar were excreted in that period. These two experiments show that more sugar is excreted when a rise in the blood sugar occurs, but that the increased output of sugar continues for some time after the blood sugar has fallen to its normal level.

This phenomenon may be explained in two ways : (1) That the kidney was damaged by the big dose of sugar and excreted sugar more easily for the next one or two hours ; (2) that the sugar does not escape from the blood passively by a 'leakage', but that an active excretion of sugar takes place and continues after the blood sugar has fallen to its normal level.

Numerous experiments have shown that the relation between the level of the blood sugar and the amount of sugar excreted in the urine is very com-

plicated. Thus the level of the blood sugar may be considerably raised without any glycosuria occurring. Von Noorden (15) states that in pneumonia the level of the blood sugar may be as high as 0·28 although no sugar appears in the urine. I have also observed this phenomenon in two cases of diabetes.

1. A man, Garrod (16), Graham (14), about 60, who three and a half years previously showed all the signs of symptoms of true diabetes, but who made a complete recovery. He is now able to eat an ordinary diet and only occasionally passes a little sugar. On two occasions the blood contained 0·28 grm. per cent. and 0·26 grm. per cent. of sugar although no sugar was passed in the urine.

2. A man (14), aged 26, who came into hospital in February, 1915, with a blood sugar of 0·50 grm. per cent. and passing 300 grm. of sugar. Under treatment he steadily improved, and the level of the blood sugar before and after meals varied between 0·29 grm. per cent. and 0·36 grm. per cent. on a day when 45 grm. of sugar were excreted in twelve hours. On the next day no food was given and the blood sugar varied between 0·27 grm. per cent. and 0·30 grm. per cent., yet only 1 grm. of sugar was excreted. Observations on other diabetics seem so show that the point at which sugar is excreted varies for each individual.

These experiments, together with those on the new type of diabetes innocens, support the view that the kidney plays an active and not a passive part in the excretion or retention of sugar in the blood.

It seems probable that in diabetes innocens the presence of sugar in the urine is due to an increased excretion on the part of the kidney. In the pure diabetes innocens of Salomon this is apparently the only lesion. But in the new type of disease this lesion is combined with a diminished carbohydrate tolerance.

Prognosis.

The prognosis of these cases is a matter of considerable importance, as it is so very different from that of true diabetes. The fact that there are probably at least three types of this disease adds some difficulties. In the type described by Klemperer the sugar has probably little significance and the prognosis depends on the kidney lesion. In the type where very little sugar is excreted the prognosis seems to be very good, for Garrod has recorded one case who remains well after seven years. Also the sister of E. B. (of this series) married and bore children with no ill effects. Salomon likewise gave a good prognosis for his cases, and the longest period he has watched one is twenty years.

A prognosis in the cases of D. W., H. H., and A. H. is more difficult to be certain about. Yet the progress of the cases seems to show that a fairly good prognosis may be given. Thus D. W. has certainly had glycosuria for five years and is still doing full work. A. H. and H. H. have been watched from the ages of eight to twelve and thirteen to fifteen respectively and are both apparently healthy children. Again, the case described by Parkes Weber probably belongs to this class and is of special interest, for the woman was in St. Mary's Hospital thirty years ago. At that time she was passing about

30 grm. of sugar a day, which was about the amount she passed in 1914. Admittedly, one would prefer to watch the cases longer before making a definite statement, but it seems fairly certain that even in the new type a favourable prognosis may be given.

Diagnosis.

A correct diagnosis is very important in these cases, as the prognosis and treatment are so very different from those of true diabetes. Although the diagnosis may be suspected from the amount and percentage of the sugar excreted, yet no certain diagnosis can be made unless a sugar test, combined with an estimation of the blood sugar, has been made. The sugar test should be applied cautiously, starting with 10 grm. If no corresponding increase in the sugar output occurs, 25, 50, and finally 100 grm. of sugar may be given. It is most important to apply the sugar test cautiously, for if the patient has a mild form of true diabetes the giving of 100 grm. of sugar might cause considerable damage. If a true diabetic, who is only passing a little sugar on a restricted diet, is given a dose of sugar of about 50 grm., he may pass the whole of it in the next few hours. Thus the giving of 45 grm. of sugar to a woman of this type caused an excretion of 50 grm. of sugar in three hours after the meal.

The greatest amounts of extra sugar excreted by any of the cases recorded in this paper are shown in Table III.

TABLE III.

		Intake.	Time.	Total Sugar.	Extra Sugar.	% of Intake.
			Hours.	grm.	grm.	
Case I		50	3	2·4	2·4	4·8
Case II		37	3	3·9	2·6	7·0
D. W.	Case III (a)	60	2½	3·75	1·9	3·1
	(b)	122	3	11·8	11·2	9·2
A. H.	Case IV	50	3	10·7	8·6	17·2
H. H.	Case V	80	4	12·6	7·0	8·7

In the old type of diabetes innocens the amount of sugar excreted is very small, but in the new type the amount may be as high as 11·2 grm., and in the case of A. H. 17·2 per cent. of the sugar eaten was excreted within the next three hours. It is advisable to estimate the blood sugar at the same time as the sugar test is made, so as to get a more complete picture of the changes taking place. The estimation of the blood sugar is not absolutely essential, but it is of great assistance in making the diagnosis. But the estimation of the blood sugar by itself is of little value unless it is estimated before and after a meal of known carbohydrate value. Unless this precaution is observed a serious error may be made. For if the patient has a mild form of true diabetes he might be passing little sugar because he was eating a restricted carbohydrate diet. In that case

the blood sugar might be within the normal limits and so lead to an error in diagnosis. Such an error has led to the relaxing of the diet in one instance that I have heard of.

Treatment.

The question arises in all these cases whether a carbohydrate-free diet is necessary. Most of the cases reported have not lived on a rigid diet and have kept well. Also A. H. and the sister of L. F. both felt ill on a strict diet and the sugar did not disappear. On the other hand, Case V of Salomon's series, a girl of ten, only passed a trace of sugar after she had been dieted strictly for one year. Riesman also reports the case of a girl of fourteen years who ceased to pass sugar under dietetic restrictions. This case is rather doubtful as the mother was apparently a true diabetic. Under the circumstances it is perhaps wiser to advise the giving of a carbohydrate-free diet for some months. If no diminution of the sugar occurs the diet may then be relaxed, although no sugar or heavy carbohydrate meals should be taken. These cases should certainly be tested from time to time.

Aetiology.

The cause of this condition is at present quite unknown, but there is some evidence to show that there is a familial element connected with the disease. Thus of eighteen cases described by Weiland, Garrod, Salomon, and those described in this paper, seven cases belong to three families and three other cases had parents or brothers and sisters who were similarly affected.

Of Salomon's cases, Case IV had a sister who was similarly affected; Cases VII and VIII were brother and sister; Cases III, IV, and V all belonged to one family and two first cousins were also affected.

Garrod's original patient had a brother who had glycosuria. Of my cases the father of D. W. occasionally passes sugar; H. H. and A. H. are brother and sister, and their father's first cousin is also affected.

There is little evidence that consanguinity has any influence, except in the cases of H. H. and A. H. Their father was the son of the marriage of two first cousins. Salomon reported the case of two families of first cousins. Here two brothers married two sisters. One family consisted of five children with three affected, while the other family consisted of seven children and two of these were affected. No other nephews or nieces, either on the father's or mother's side, were affected. Apart from these considerations, there is no evidence as to the causation of the disease.

Conclusions.

1. An innocent type of glycosuria occurs which is not associated with renal disease.

2. There are at least two types of this disease :

(*a*) Where the output of the sugar is very small and is not appreciably altered by a dose of sugar.

(*b*) Where the output of sugar is rather greater and is increased to a certain extent by a dose of sugar : the level of the blood sugar is also appreciably altered by the dose of sugar.

3. The relation of the amount of sugar excreted and of the amount of sugar in the blood suggests that the sugar is actively excreted by the kidney.

4. The prognosis is good.

5. The diagnosis should only be made after careful sugar tests.

I wish to express my thanks to Dr. A. E. Garrod for allowing me to work on his cases and for his constant help and encouragement.

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ON GUNSHOT WOUNDS OF THE CHEST AS SEEN AT A BASE HOSPITAL IN FRANCE

BY A. B. SOLTAU AND J. B. ALEXANDER

THE purport of this paper is to deal with the clinical aspects of the cases of gunshot wounds of the lung which have come under our care during the five months from July to November 1916, avoiding any discussion as to certain academical points and any theorizing on the little understood physical problems involved.

Classification.

Gunshot wounds of the chest may be broadly divided into two classes—non-penetrating and penetrating. Under penetrating wounds are included those which are 'entrance only' and those with 'entrance and exit'. The character of wound naturally depends on the projectile, and large shell fragments may cause a very excessive tearing both of thoracic wall and of lung tissue. The nature of the wound produced by a bullet will also vary very greatly with the range at which the man was hit. At both short and extreme ranges 'explosive' effects are sometimes seen, due in part to the tremendous initial velocity of the bullet, and in part to the short axis rotation described below. In its flight, in addition to the forward movement, a bullet has a rotatory movement around its long axis from the spin imparted by the rifling. A further rotation takes place, with the modern bullet, around its short axis should any resistance be met. The result is that the bullet is at one moment travelling broadside on after it has encountered the resistance, and this will greatly increase its destructive powers. This rotation takes place at short ranges when the velocity is very high and disappears at about 600 yards when the bullet has settled into its flight, reappearing towards the end of the trajectory at long range. Hence the severity of the wound may vary considerably with the distance of the firing point from the man injured. A study of many head wounds seen in the first twelve months of the war exemplified this short axis rotation markedly, the wounds received in the communication trenches and the firing trench being more explosive and generally destructive than those received on the roads immediately behind, which latter wounds were more usually clean through and

through.   Another possible factor to remember is the cushion of compressed air which surrounds the head of the bullet and which is visible in instantaneous photographs.   This cushion may be responsible for some cases of penetration with no apparent lesion, as mentioned later.   The striking force of the modern bullet is enormous, and little wonder can be felt at the severity of the damage it inflicts.   Working on the formula $\text{Energy} = \dfrac{\text{mass} \times \text{velocity}^2}{2}$, the striking force of the Mauser bullet, weighing 154 gr. and with an initial velocity of 2,900 ft. per second, can easily be calculated.

Non-penetrating Wounds.

From the striking force of a non-penetrating missile the underlying lung is at times damaged, and the extent of the damage may vary considerably.   It may cause a simple haemoptysis with no physical signs.   This condition is usually of short duration and has not been seen to leave any permanent defect, though the possibility of lighting up latent tubercle must be remembered. We have had eleven such cases of haemoptysis without physical signs.   At times, however, the after history of the case, with a prolonged haemoptysis, suggests that some congestion has developed, though no appreciable physical signs have been elicited.

A true concussion pneumonia, as met with in civil practice, is by no means uncommon, and follows the ordinary course of the disease.   Such a condition rarely causes anxiety, and it is not accompanied by severe constitutional symptoms.

Lastly, these injuries sometimes cause collapse of the lung on the injured side, which may vary from partial deflation to a massive collapse of a whole lobe.   It is at times accompanied by a contra-lateral collapse, massive or partial, and occasionally whilst the lung on the injured side apparently escapes, yet contra-lateral collapse has been observed.   The mechanism of production of this condition is dealt with later.   Here again one is struck by the comparative rapidity of disappearance of the signs and the absence of any permanent ill effect.

Penetrating Wounds.

'Entrance' wounds and 'entrance and exit' wounds will be considered together under the above heading, for the signs in each class are largely similar, though they may vary in degree.   An entrance wound alone, however, must be regarded generally as more serious, owing to the retention of both the foreign body and of fragments of clothing and equipment carried in thereby. The quantity of such clothing sometimes recovered from a wound is surprising, and the retention of quite a small particle often accounts for prolonged sepsis.

Before passing on to discuss the dominant features of these wounds reference must be made to those puzzling cases, of which we have seen five, in which, from

the position of the wounds, a lung must have been perforated and yet no physical sign of injury is apparent. This may be explained in various ways:

(a) As an interlobular penetration, the air cushion acting as a soft buffer which forcibly separates the lobes ahead of the track of the missile, just as it is supposed to do in saving nerve trunks and vessels from injury.

(b) As an effect of the heat engendered by friction in passing through the tissues, which, acting as an immediate searing agent, closes both small vessels and alveoli.

From what has been previously said about oscillation it is obvious that this non-damaging penetration is more likely to occur at medium ranges, say from 600 to 1,200 yards.

The three dominant conditions which may arise from a penetrating lung wound, either singly or in association, are haemothorax, pneumothorax, and collapse. These will be considered now in more detail.

Haemothorax.

The presence of blood in the pleural cavity is, it is now generally accepted, due in the majority of instances to injury not of the vessels of the thoracic wall but of those of the lung itself. It is a comparatively frequent condition, and in our series of 139 cases was present in varying amount in eighty cases.

The size of the haemothorax varies within wide limits from so small an amount as to be perceptible only on the closest examination up to a complete filling of the pleural cavity. The apparent severity of the wound is no criterion of the amount of the effusion. What, therefore, is the factor which determines the limitation of size? An explanation to cover all cases must not be sought on purely physical grounds, for the highly complex physiological actions of the lung and its little understood innervation must be regarded as all-important contributory factors. Until the latter are better understood it is only possible to theorize. Undoubtedly the mechanical effect of pressure of the effusion will tend to check haemorrhage, but not until an effusion large enough to collapse the lung and so occlude the bleeding points has been poured out. With an injury involving the base of the lung a small effusion will be sufficient to cause deflation of that base, but where the upper part of the lung has been wounded a very extensive effusion would be required. To account for the limited effusion frequently seen with the latter kind of wound a further cause must be sought, and apparently this is afforded by active collapse, either massive or a partial deflation.

The well-recognized signs of fluid in the pleural cavity need not be touched on, but misleading ideas as to the amount of fluid present will arise unless the closest attention be paid to the interpretation of these signs. More especially would we emphasize the position of the apex beat and also that of the diaphragm. For the determination of the latter point an instantaneous X-ray

photograph, taken through an intensifying screen, is of great value. In simple haemothorax the dome of the diaphragm is at a higher level than the normal, contrary to what would be expected on physiological grounds, seeing that experimental injury to the lung is followed by increased diaphragmatic tone, and hence a lowering of the dome. It is impossible at present to say why gunshot wounds should show this extraordinary difference from those produced in the laboratory, but, whatever the reason, the elevation of the dome can only mean that instead of an increase of pressure within the pleura, which would be expected as the result of an effusion, the pressure is actually diminished and therefore the lung collapsed. Since, therefore, this collapse is not the result of the pressure of the effusion, it must be due to some independent process. Its effect is to stop the haemorrhage because the vessels collapse with the lung tissue. In fact, we are led to regard collapse as nature's pulmonary haemostatic. An examination of the case sheets collectively has strengthened the opinion— formed at first in isolated cases—that a small haemothorax is often associated with a considerable degree of deflation of lung, indicating the controlling action of the latter process.

The important question of clotting of the haemothorax must be considered, in that the line of treatment to be adopted is closely associated with this. That clotting does take place—contrary to physiological expectation—must be admitted, but both the degree and the nature of the clot vary considerably. Certain varieties of clot are described in the official 'Memorandum on the Treatment of Injuries in War'. These, however, are not commonly met with. The usual experience, on examining a chest post mortem, is to find a blood-stained fluid which contains small particles of clot in the dependent areas. The remaining fluid usually does not clot, or only partially so, even after standing, a proof that the fibrin has been deposited. We have frequently, for purposes of examination, drawn off what appears to be blood, which after prolonged standing has not clotted, and the inference is that we have been dealing with blood already defibrinated, and therefore not capable of forming a massive coagulum. The presence of sepsis—and it is difficult to believe that some mild degree of sepsis is not present in most cases—may be one of the factors in preventing a complete coagulation, and Sir John Rose Bradford, who can speak with more authority than any on this subject, suggests the constant movement of the lung as another deterrent. Our limited observations would indicate that a partial clotting, or at any rate a deposition of fibrin, is constant, but that a true massive clot is extremely uncommon. This fibrin deposit fortunately does not usually lead to extensive adhesions, with subsequent great limitation of lung expansion. The time at which the process of clotting or the deposition of fibrin commences is not as yet determined. Early observations tended rather to regard it as a late occurrence, but an increasing volume of evidence is accumulating to prove that the process commences at a very early time after wounding. Investigations now being carried on by Sir Wilmot Herringham and other observers may shortly enable them to make an authoritative statement.

Pneumothorax.

Whilst not so common as haemothorax, the occurrence of pneumothorax is yet comparatively frequent in cases seen at the Base. Amongst our series of 139 cases this condition has been present in thirteen, in five associated with 'entrance' wound, and in eight with 'entrance and exit'. It is rare to find free air in the pleural cavity, unaccompanied by a haemothorax. In one case, however, which went to section, a bullet had traversed the lung, causing complete collapse and a large pneumothorax, but no haemorrhage. The patient died of a pneumococcal infection, the injured pleura being covered with lymph and containing a small amount of serous fluid, whilst the uninjured lung showed early pneumonic changes, and commencing pericarditis was also present. It is usual to find only a moderate amount of blood when air is present.

Before proceeding to discuss the causation of pneumothorax, it is necessary to divide the cases into two classes—those occurring immediately or very shortly after injury, and those arising later on. Briefly, in the former category we are dealing with air in the pleural cavity, and in the latter, in nearly all instances, with gas, and of course therefore with a far more serious complication.

In the early cases the problem has points of similarity to that of the causation and limitation of haemothorax. The intrapleural air does not usually gain access through the parietal wound, which is often so valvular as to be immediately self-sealed. Further, a certain amount of experimental evidence goes to show that opening the pleural cavity in life does not necessarily cause collapse of the lung, with consequent drawing in of external air. The air of the pneumothorax we believe to be mainly intrapulmonary in origin. Presumably in all cases of tearing of lung tissue some air escapes, but it is only when it is considerable in amount that it becomes obvious. The conservative collapse of an injured lung, already discussed, would appear to come again into force, and by its constricting effect to occlude the leaking air passages. When, however, a considerable bronchus with a rigid wall is injured, even extreme collapse may not be sufficient, against the force of inspiration, to stop the leak, which then goes on until the pleural cavity is distended with air at a pressure equal to that of the highest intrabronchial respiratory wave. To use a common simile, a valve-pump condition is set up through the injured bronchus, which permits air to enter the pleural cavity until the pressure in the latter is equal to that in the bronchi.

Once a pneumothorax has been made and the equilibrium established between the collapsing lung acting as a throttle and the intrapleural air, whether the amount of the latter be small or great, it does not in our experience tend to increase. Absorption rapidly takes place, and it is no uncommon thing to find a fairly extensive pneumothorax disappearing within four or five days. Of the classical signs of the existence of intrapleural air we need not speak as they are known to all.

Before passing on to the gas pneumothorax brief reference to the rare cases of late air pneumothorax must be made. Even so long as three weeks after the wound, when apparently conditions are clearing up, air may suddenly appear in the intrapleural cavity. At times this is due, as in civil practice, to a tuberculous focus, which the injury has lighted up, becoming active and leading to a pulmonary fistula. In other cases, as a haemothorax has absorbed and a collapsed lung has expanded, the old wound of the lung has given way, and a pulmonary fistula has so been established; in fact, a secondary 'pneumorrhage' has occurred.

So far as experience at the Base goes the presence of an air pneumothorax has rarely given anxiety. By the time the patient has reached the Base his cardiac mechanism has usually adjusted itself to the dislocation caused by the air pressure, and even a considerable displacement has not markedly embarrassed circulation and respiration. This proviso must, however, be entered, that a left pneumothorax is more likely to embarrass than a right, and therefore needs more watching and frequent determination of the physical signs, so that prompt release of the air by puncture may be carried out if necessary.

Presumably a left pneumothorax is more serious, in that the resulting cardiac dislocation to the right involves greater disturbance of the large vessels at the base.

Coming now to the second class of case, that produced by gas in a pleura, whether apart from other conditions or associated with a simple haemothorax or with an already existing haemo-pneumothorax, it is obvious that a very grave complication has ensued. The sudden appearance or increase of intrapleural air, evidenced by rapidly increasing distress, must be viewed with the greatest alarm. It is an evidence of sepsis in an acute form, by infection with the *B. aerogenes capsulatus* or other gas-producing organisms. A prognostic sign of the advent of this condition has been described, namely, the existence over a haemothorax of small patches of Skodaic resonance, suggestive of a localized collection of gas.

The rapidity of onset of this condition, more usually seen in cases of 'entrance' wounds, is an argument in favour of cases reaching the Base as early as possible before its advent. We have had at least two cases who had this infection on arrival, presumably developing *en route*, and they were not amongst those who were sent down shortly after being wounded.

One other air condition must be mentioned, surgical emphysema. This is relatively common, occurring in 15 per cent. of our series. It is of very little moment and soon disappears, nor have we seen any ill effects beyond the added difficulty it causes in auscultation. It may spread over the greater part of the body, but is usually confined to the injured side of the thorax. As a matter of clinical interest and prognosis, we have been inclined to regard its presence as a favourable sign, looking upon it as a safety-valve, preventing the formation of a pneumothorax, which has only rarely been found coexisting.

Collapse.

By the term collapse a process of deflation of the lung is indicated. Such deflation may be partial or complete, and all stages may be met with up to the massive collapse described by Pasteur, the physical signs naturally varying with the degree of the process.

Civil experience had not led us to expect the frequent occurrence of this phenomenon, and we were surprised to find how common it was in association with battle casualties. At first it was difficult to believe that our interpretation of the physical signs was correct, and it was only the cumulative effect of experience that led us to regard collapse as an almost necessary concomitant of a wound of the lung.

As has been said, the degree of deflation varies, and whilst it is impossible to give accurate statistical information as to the degree, yet roughly it may be stated that 48 per cent. of the cases showed deflation to a greater or less extent.

The evidence of collapse varies according to the presence or absence of haemothorax. Where there is no haemothorax the physical signs are as follows: Over the area of massive collapse there is complete dullness on percussion, with absence of breath sounds, vocal resonance, and tactile vocal fremitus to a degree simulating fluid. Associated with this there is dyspnoea, exaggerated on exertion, and cyanosis. So close is the resemblance to fluid that on several occasions the exploring needle was used, without however finding any fluid. Further, the 'feel' to the finger is not that of fluid, and the cardiac displacement, if any, is towards and not away from the affected area, whilst the rapidity with which the signs may disappear is contrary to all experience of the rate of absorption of an effusion. Where the deflation has not been so complete a condition of impaired resonance is found associated with a tubularity of breath sounds and an increase of vocal resonance and tactile fremitus, and at times some crepitation. In such cases the question arises whether the condition is not that of pneumonic consolidation; in fact, the physical signs would naturally suggest the presence of a pneumonic patch. But the absence of the constitutional signs of a pneumonia and the rate of disappearance contra-indicate this. Moreover the arch of the diaphragm is drawn up and the heart is displaced, neither of which conditions is produced by pneumonia. A further proof may be adduced, that in those cases where we had time to estimate the chlorides in the urine there was no diminution in their quantity.

In cases where haemothorax is present the signs of collapse are obscured by those of fluid. But here the employment of X-rays shows that the arch of the diaphragm is raised, and therefore that the lung has shrunk to a greater degree than the pressure of the fluid could have accounted for. There must in such cases be some other cause than pressure to produce collapse of the lung. It is suggested that the process is due to nerve influence, and that, owing to the injury which the terminals of the vagus in the wounded lung have sustained,

a reflex action is set up. The reflex path would be from the terminals, via the vagus, to the respiratory centre, and thence by the phrenic nerve to the diaphragm, causing a diaphragmatic paralysis. This would explain the raising of the dome of the diaphragm of the injured side, and the collapse of lung. Other observers have noted cases in which the appearance of the diaphragm as seen through a wound suggested from the lack of tone a complete paralysis. The effect of such paralysis, with consequent collapse, would be to limit the effusion of both blood and of air into the pleural cavity.

One of our cases showed the value of collapse as limiting haemorrhage. The lung was extremely deflated, resonance being impaired up to the spine of the scapula, but only a comparatively small haemorrhage was present. Yet the degree of collapse would have permitted at least three times the amount of fluid to occupy the pleural cavity.

Before leaving the subject it may be mentioned that collapse most usually occurs in the lower lobe and in the posterior part of the lung, producing a wedge-shaped area, with its apex upwards, and reaching commonly to the lower angle of the scapula.

Reference must also be made to the rapid alteration which takes place in the physical signs of collapse. We were fortunate to receive many cases which Col. Sir Wilmot Herringham had seen at the Central Clearing Station, with which he sent down the notes of their condition as seen by him. Even in the period occupied by the journey their condition had frequently changed. Whereas he noted only weak breath sounds, we found a loud tubular breathing with increased vocal resonance and tactile vocal fremitus. Probably an extreme collapse had taken place and the lung was just beginning to re-expand. When the patient arrived at the Base this process of expansion had reached a further stage, and we were able to watch that lung steadily expanding to the full degree, the tubularity disappearing and the normal vesicular murmur taking its place. Had a still earlier note been made it is surmised that a total absence of any breath sounds would have been discovered, and that a primary massive collapse to overcome the injury had then existed, and, as the need became less urgent, the normal condition was gradually resumed.

Contra-lateral Collapse.

Associated with the collapse of the injured lung attention was early focused on to a condition frequently existing in the undamaged lung. Briefly this condition was as follows : An area of comparative dullness involving a variable portion of lung usually in the opposite base, associated with altered breath sounds, mainly a tubularity of breathing, with increased vocal resonance and tactile vocal fremitus. This at first suggested a broncho-pneumonic condition, but the absence of constitutional symptoms and the disappearance without any moist sounds rather negatived this. It ultimately was obvious that we were dealing with an associated condition of collapse of which the causation

was not clear.   Was it due to aspiration of blood, producing patches of collapse, as in broncho-pneumonia?   This was negatived because of the circumscribed area and the absence of any moist sounds.

Then the question of its being a compression condition in Grocco's area naturally suggested itself.   In certain cases, with large effusion undoubtedly, the transmitted pressure with the signs in the areas known as Grocco's triangle does occur, and perhaps more so in gunshot wounds of the chest than in ordinary pleural effusion as seen in civil practice.   Accepting the explanation that this paravertebral dullness is due to mediastinal displacement, and that it is increased when the patient lies on the healthy side, it is likely to be frequently seen in battle casualties, where from the nature of the wound the patient cannot with comfort lie on his injured side, thus departing from the conventional attitude of leaving his undamaged lung uppermost.   But this explanation does not cover all cases.   Firstly, the area is too great, and in many cases does not conform to the paravertebral triangle.   Secondly, it occurs where no fluid is demonstrable on the injured side, or where its bulk is not sufficient to account for the increased dullness.   Again, it is not due to transmission by spinal resonance, because of the increased vocal resonance and tactile vocal fremitus.

Hence a further explanation must be sought, and in the absence of other evidence we would suggest that here again nerve influences predominate, and that the condition is due to a reflex action from the vagus terminals to the respiratory centre, and thence by the phrenic to the diaphragm on the uninjured side, causing deflation up to total collapse.

Further observations will probably show that this condition prevails far more frequently than at present suspected.   For instance, twenty-four definite examples of contra-lateral collapse were noted in the series, or 17 per cent.

Septic Infections.

The greatest danger, once the primary shock is overcome, in lung wounds is undoubtedly the advent of sepsis.   As has already been pointed out, the danger is greater in ' entrance ' wounds.   It has occurred in our series in thirteen cases.

To recognize the advent of sepsis, too much attention must not be paid to conventional teaching.   A frequent examination of the chest is essential, and is of far more importance than a mere slavish watching of the chart.   Early recognition of sepsis with prompt treatment may well cut short convalescence by many weeks.   Bacteriological examination of an aspirated sample of the effusion is often misleading, as the infection may be localized and the sample drawn off be free from contamination.

The leucocyte count also cannot be relied on implicitly because of the disturbing factor of inflamed wounds, and if delay be made for repeated counts the mischief may become far advanced.

The aspect of the case must be regarded as a whole—facies, distress, pulse rate, temperature, alteration in position of apex beat, development of signs

indicative of gas, and especially respiration rate; and the combination of suggestive signs demands prompt action.

Such then are the predominant conditions as we have seen them in gunshot wounds of the chest, involving the lung.

Before touching on the treatment adopted it may be helpful to refer to some temperature charts illustrating the course followed in typical cases.

I. A typical haemothorax follows a steadily improving course. The initial fever gradually subsides, each diurnal oscillation being less until the mean is arrived at.
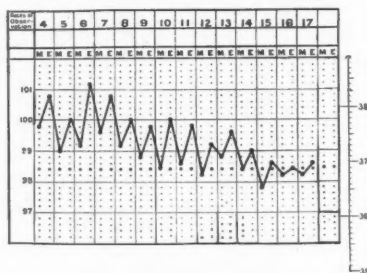
CHART I.
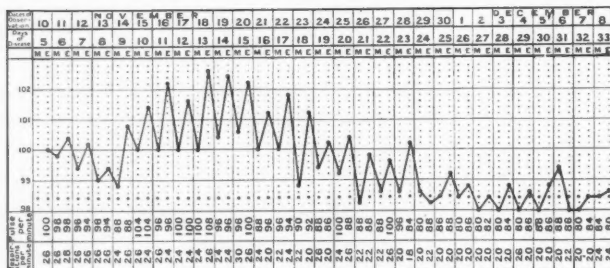
CHART II.

II. A secondary curve is frequently seen with haemothorax after the temperature has approached the normal. It is characterized by what we have termed the 'periscopic' course, in that a steadily increasing morning and evening rise takes place. This reaching its maximum, similarly decreases till a final normal mean is reached. The regularity of the increase is remarkable and is so characteristic that it has sufficed to differentiate this rise from that of sepsis. The chart illustrated is typical but prolonged, as usually this course lasts for about eight days only. (The term 'periscopic' was suggested to us by the trellis-work metal extension which carries the observing mirror in so many trench periscopes.)

III. Whilst bearing in mind that a temperature chart is not an infallible guide to sepsis, it may be helpful to include two which indicate the onset of this complication. The first example is self-evident. The second would not have

caused alarm but for other signs, especially the pulse, and yet in this that grave complication, gas infection, was present. The patient was at first apparently following the normal course of a haemothorax. On the day before that marked 'Sepsis' a small resonant area was noted over the haemothorax. On the day after the pulse jumped to 140 and the respiration to 40, and immediate resection was performed. Probably the rise eight days earlier was really a mild infection which was being overcome until the 'gas' organism became active.
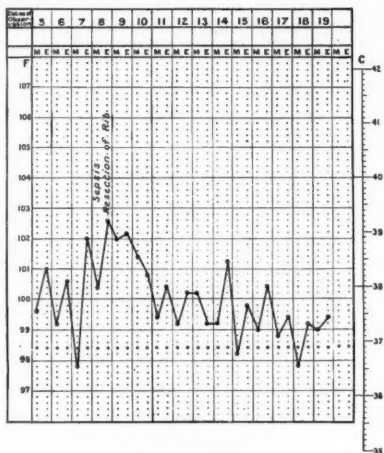
CHART III A.
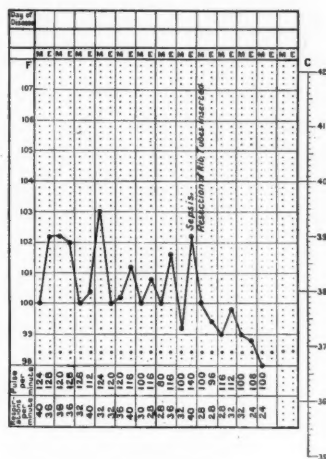
CHART III B.
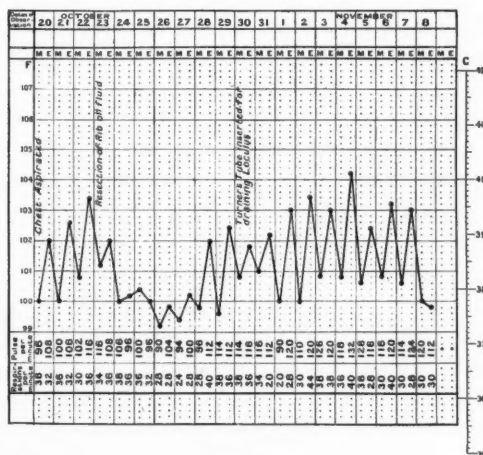
CHART IV.

IV. After resection for infection, a temperature showing marked oscillations is often seen. This is merely due to absorption from an infected surface, and provided that drainage is adequate need cause no alarm. It demands, however, the ordinary surgical treatment of an infected cavity by douches, &c.

Intercurrent disease must not be overlooked, as it may profoundly modify the progress of the case. Tubercle, presumably a latent infection roused to activity by the trauma, may be met with, and when a case presents some unknown factor which does not conform to the ordinary course this condition should be sought for.

In two of our cases which showed little progress, the ultimate finding of tubercle bacilli elucidated the problem. Again, pneumonia may occur, and where a man has been left lying out untended for from one to four days, especially in the winter months, it is not surprising that this complication occasionally arises. A puzzling case, where apparently the lung condition had completely cleared up and yet the man was far from well, was finally found to be a paratyphoid infection.

Finally, that unknown and yet all-prevalent infection, known provisionally as 'trench fever', cannot be ignored. Its characteristic temperature curve with the relapsing spikes of pyrexia may at first cause alarm until the real nature of the infection is realized.

Prognosis.

Being in ignorance of the progress of cases after they leave the Base for England, no attempt can be made at an ultimate prognosis, and the recording of final results must be left to those who are in charge in the English hospitals. It may be said that, so far as we know, a simple haemothorax recovers completely, with practically no pulmonary impediment. A non-infected pneumothorax equally does well. The advent of sepsis in either condition, necessitating resection and the draining of an empyema, naturally constitutes a grave impairment to the efficiency of the lung, and probably the ultimate result is much as in civil practice.

Treatment.

The preceding paragraphs have suggested to a certain extent much of the treatment adopted, but certain points need discussion.

Haemothorax. The essential question here is 'Should surgical interference be adopted?' For the large effusions, so considerable as to dislocate and embarrass the heart, naturally the answer must be 'Yes', and at as early a moment as practicable. It has been laid down that this can be safely done seventy-two hours after injury without any risk of renewal of haemorrhage. The right method to adopt is yet indeterminate. In certain cases the excision of the wound, the resection of a rib and the washing out of all the pleural contents, and complete closing of the wounds has been described as giving excellent results, but we have no personal knowledge of this method, which demands a high degree of surgical skill. More commonly, aspiration of a sufficient quantity of blood to render the patient comfortable is the method used. Both

these procedures, however, are those to be followed at the Casualty Clearing Station, as naturally such cases are not fit to travel to the Base until something has been done to relieve them.   The remaining cases, forming a considerable proportion of the total, are those with a moderate effusion, whose treatment has to be decided on at the Base.   It has been urged that all such should have the blood aspirated with oxygen replacement, owing to the risk of sepsis or of the formation of adhesions which will hamper the future expansion of the lung.   Sepsis, however, is not, in our experience, a sufficiently frequent occurrence as to demand routine aspiration.   From post-mortem findings adhesions are not very constant, nor yet very dense.   Lastly, the satisfactory manner in which a haemothorax does absorb, and that completely, leaving a lung expanding freely and fully, appears to be a sufficient reason for not interfering in the majority of cases.   Should absorption be delayed aspiration with oxygen replacement would be the best course to follow, but we have rarely found it necessary to do this.

Pneumothorax.   The general principles laid down for haemothorax apply equally here.   In certain early cases, where a bronchiole, too large to be collapsed, is laid open, air will be pumped into the pleural cavity until grave embarrassment results.   This is less frequent than might be expected, owing to the external wound acting as an outlet valve, either directly or into the tissues. With no such outlet repeated puncturing to release the air, or resection, will be needed.   This again is a problem mainly met with at the Casualty Clearing Station.   In other cases puncturing can rarely be necessary, for the air is quickly absorbed.

For the gas pneumothorax the treatment becomes one of dealing with a septic infection.

Sepsis.   There is only one line of treatment for this grave complication, resection of part of a rib, and the establishment of free drainage.

Initially, where great collapse of the patient exists, and it is doubtful whether he will stand the shock of this operation, it is well to drain the pleura by means of a Turner's trocar ; but this should be regarded as a temporary expedient to be followed up by later resection when the patient's condition permits.

The selection of the site for resection, determined naturally by the position of the wounds, should give the best drainage.   At the operation limiting bands of adhesion are often found, which quite possibly are walling off loculi of infected material.   These commonly break down later, but if they do not then the separate loculi must be opened and drained.

In all these surgical proceedings a local anaesthetic is indicated.   The extreme respiratory excursion induced by a general anaesthetic is dangerous, and the added risk of anaesthetic dangers must be avoided.   To illustrate the point, one patient who had a bullet wound of his right lung made an apparently complete recovery.   Subsequently he had a general anaesthetic for the removal of the bullet from his abdominal cavity, where it had been located.   He was

rather excited during anaesthesia.   Next day his temperature rose to 103° and
he was profoundly ill.   The abdominal condition was entirely satisfactory, and
after four days a small pocket of pus was found in his left pleura, which could
not have been involved in the wound.   The suggestion was that he had aspirated
into his left lung from his injured right lung some infected material which set
up a septic broncho-pneumonia with subsequent empyema.

Once drainage is established the case can be treated as an ordinary empyema.
Reference has been made to the rather alarming temperature which may develop,
as when any large septic collection is drained.   For this condition irrigation
with eusol and injections of iodoform emulsion are very helpful.

As a general routine in all cases of lung wounds, anti-tetanic serum is
given each successive eighth day until healing is well in progress.   Since
this has been done we have seen no case of tetanus following a wound of the
chest.

Before leaving the question of treatment, the problem of the removal of the
foreign body must be considered.   It has been our practice to have all foreign
bodies localized by X-rays as soon as possible.   If localization proves that a foreign
body is near the surface, it is removed under local anaesthesia when the lung
condition has cleared up, but we are never in a hurry to do this.   If, however,
it be buried 'deep' in the thoracic cavity no attempt is made to search for it,
unless indications of focal infection appear, as experience shows that harm does
not frequently follow.   We have notes of only two cases where it was deemed
necessary to remove a deeply lodged fragment.   But it is a matter of military
importance that the patient should not know anything of the presence of a foreign
body, as it may be the pretext for future malingering.   One such example came
under our notice, where a man who had been shot through the chest was left
with a bullet which was lodged close to the angle of the ninth rib.   He 'went
sick' as soon as he was returned to the front, with vague pains around his
heart, near the site of entry, which were alleged to be due to the bullet, and his
statement could hardly be disproved until localization had been carried out.
The bullet was then removed and his symptoms were all cured.   Surgeons at
home may not have realized the possible difficulties caused by leaving foreign
bodies, which their colleagues at the field will have, with imperfect knowledge
of the conditions existing, to deal with.

It is hoped that these clinical observations, put together at the request
of Col. Sir W. Herringham, somewhat hurriedly in the midst of the active work
at a Base Hospital, may be of some value as a contribution to the current
medical literature of the war.

Appendix.

Total number of *cases* 139

    Haemothorax, large 2

           „   small or medium [1] 78

    Pneumothorax 13

    Collapse, alone 31

    Non-penetrating wounds with haemoptysis . . . 11

    Penetration with no physical signs 5

    Concussion pneumonia 1

Sepsis occurred in 13 cases as follows :

    Following haemothorax (of which 4 were characterized

        by sudden gas formation) 10

    Following pneumothorax 2

    With gangrene of lung 1

Mortality. Total 10, or 7·1 per cent., as follows :

    From secondary peritonitis (probably pneumococcal) . 1

       „   pneumothorax and associated tuberculosis . . 2

       „   haemothorax and broncho-pneumonia . . . 1

       „   gangrene of lung 1

       „   haemothorax and tetanus 1

       „   haemothorax with pneumonia and pericarditis . 1

       „   pneumothorax (1 a few hours after arrival) . . 2

       „   pyohaemothorax with subphrenic abscess . . 1

Contra-lateral collapse noted in 24 cases.

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[1] A haemothorax is regarded as medium sized where dullness does not extend above the lower angle of the scapula, nor farther forward than the mid axillary line.

CLINICAL OBSERVATIONS ON THE EFFECT OF DIGITALIS IN HEART DISEASE WITH THE PULSUS ALTERNANS

By J. DAVENPORT WINDLE

In this paper I purpose to consider briefly some effects of digitalis on the pulse and symptoms in cases of heart disease with the pulsus alternans; my object being to show that digitalis does not deserve the ill repute it bears for the treatment of these cases.

The recital of some elementary considerations concerning the pulsus alternans is a necessary preface to the subject, since the specific characters of the pulsus alternans are not as yet common knowledge. In most text-books on general medicine the descriptions of the nature and significance of the pulsus alternans evidence a neglect of verifying original references, since the term is used indifferently for many forms of pulse rhythm which have other characters and causes.

I.

A tracing of the pulsus alternans is characterized by the sequence of a strong and weak pulse which follow each other at equal time intervals, or the weaker pulse may occur a trifle late, but since the delay is no more than one-tenth of a second, it is too short to be appreciable by touch, so that clinically the rhythm of the pulsus alternans is always a regular one.

It is necessary to emphasize these specific time relations of the pulsus alternans in order to distinguish it from more common pulse rhythms having variations in strength, which are sometimes closely like the pulsus alternans, and with which they are frequently confused. In clinical works the terms ' pulsus alternans ' and ' pseudo pulsus alternans ' are still sometimes used to designate the irregularities in pulse force, which result when an extra-systole, causing a feeble pulse, succeeds each normal beat; and for the yet greater disparities in rhythm and force present in the completely irregular pulse of auricular fibrillation. For diagnosis it is all-important to recognize that the feeble beat of the pulsus alternans does not occur prematurely under any circumstances, and that the pause after it, although it may be a trifle shortened, is never prolonged. A pulse rhythm of the first kind just mentioned, that is to say extra-systolic bigeminy, not uncommonly ensues in patients under the full

influence of digitalis, and in consequence of its confusion with the pulsus alternans, the misconception has arisen that digitalis has the power of causing the pulsus alternans.

The regularly recurring and alternately strong and weak contraction of the ventricle, which causes the pulsus alternans, is ascribed to impairment of the contractile function of the heart muscle. While such a view of the essential nature of the phenomenon admits of doubt, yet the theory is quite in accord with the symptomatology and clinical course of heart disease cases which show the pulsus alternans, and there is abundant experimental and clinical evidence which makes it warrantable to speak of the pulsus alternans as being invariably the expression of an overtaxed heart.

Alternating heart action occurs in experiment under various conditions which lead to exhaustion of the heart; thus, if a healthy heart is made to contract sufficiently rapidly by throwing in induction shocks at a rate it can barely follow, the contractions invariably become alternately strong and weak when a certain rate is attained. Under the influence of some poisons, or if the heart is exhausted by long experiment, alternation in strength of the ventricular contractions may ensue spontaneously when the rate of the heart is slow, or it can be readily induced if the rate of contraction is slightly increased, or if the rhythm is altered by inducing a premature beat. On these considerations and others it is needless to discuss, the important conclusion is reached that the pulsus alternans signifies disproportion between the contractile power of the heart, and the rate at which it is beating; or expressed in another way, the slower the rate of the pulsus alternans, the greater the degree of exhaustion it implies.

The pulsus alternans is met with in patients under like conditions to those of experiment; it occurs, for example, not uncommonly in paroxysmal tachycardia, particularly if the attack is of long duration; in acute toxic diseases, notably croupous pneumonia, and in severe heart failure from rheumatic lesions, but its most frequent association is with widespread and advanced arterial disease in aged people. This combination of arterial disease and the pulsus alternans is occasionally present for weeks or maybe a few months without obtrusive symptoms referable to the heart,[1] but when such is the case it can be predicted that, sooner or later, severe heart failure and dropsy will inevitably ensue. This has been the course in all such cases under my own care; the average duration of life, in those I have observed, from the inception of the pulsus alternans has been about two years, in a few cases three years. The importance of the pulsus alternans for prognosis is thus very great; it is the only form of pulse rhythm which, in itself, gives definite information about the functional efficiency of the heart; whether it furnishes indications for treatment, or how far it is susceptible to the influence of drugs, are questions which as yet have received but little attention.

[1] In one patient under my care for enlarged prostate the pulsus alternans was present for over four months without breathlessness or any symptoms referable to the heart.

II.

Alternating heart action has been observed in animals poisoned by digitalis, but there does not appear to be convincing evidence that this drug or any other acts specifically in causing alternation. It is stated that when digitalis is given to patients in sufficient doses the drug occasionally induces the pulsus alternans. These considerations are the basis of the prevalent opinion, that if digitalis is given to patients with heart disease who already show the pulsus alternans, both the alternation in pulse strength and the patients' symptoms are likely to become worse under its use; it is argued that since impairment of the contractile function of the heart muscle is the cause of the pulsus alternans and this pulse rhythm ensues in experiment and at times in patients as an effect of digitalis, then it is probable, if the pulsus alternans is present, the administration of digitalis may depress still more the already impaired function of contractility which it expresses, and thus lead to increased alternation of the pulse; moreover a further supposed contra-indication to the use of the drug is furnished by its constricting action on the arteries, which by increasing the peripheral resistance to the heart will in turn augment its exhaustion.

My own experience of the clinical use of digitalis does not support these assumptions. On the contrary, it indicates that the drug has little, if any, power to bring about the pulsus alternans in healthy or diseased conditions of the heart; and that in cases of heart disease in which this form of pulse is present, there is no evidence that digitalis increases the irregularity; on the other hand, it frequently has the opposite effect, that is to say, the pulses become more equal in force and not uncommonly disparity in strength of the beats is temporarily abolished under the use of the drug, and the patients' symptoms for the time being are improved in all respects; moreover these good results not seldom ensue coincidently with a considerable rise in the blood pressure.

Since the pulsus alternans is evidence of an overtaxed heart, we should expect the alternation in force of the pulses to continue as pronounced, or become more pronounced with increased peripheral resistance to the heart, and to become less decided or abolished with its decrease, always providing that the changes in blood pressure were great enough and lasting to further embarrass or to relieve the work of the heart. It is a fact, however, that such relations are not constant; it is evident in some of the tracings which follow that the pulse of the same patient may show pronounced alternation when the blood pressure is low, while the pulsus alternans is absent when the blood pressure is considerably higher. It must be said, however, what a change in blood pressure alone may exert on the persistence and degree of alternation in strength of the pulse cannot certainly be determined clinically, because there are no means of altering the blood pressure to an effective extent without at the same time varying other factors in the circulation, which not improbably may together nullify the adverse or favourable influence which a variation in blood pressure alone would exert. Of the factors which influence the persistence, increase,

decrease, or abolition of alternation, the rate of the heart is the most potent; in the same patient it is a rule to find alternation increased with an increase, and decreased with a slowing in pulse-rate, and not infrequently in a given case there is what may be termed a critical rate of pulse, about which changes in pulse strength occur; that is to say, if the pulse-rate rises or falls below this, alternation ensues or is lessened or abolished; thus in one patient the pulsus alternans may only be shown when the rate is over 100 per minute, while at anything below this it is absent; in another case the pulsus alternans may persist with a rate of 80, yet disappear at 75 per minute, and these changes in character of the pulse occur irrespective of the height of the blood pressure.

It is notable in most cases of myocardial and arterial disease with the pulsus alternans that the blood pressure is, as a rule, an abnormally high one; there is also a further association, namely, a close correspondence between the well-being of the patient and the maintenance of a certain height of the arterial pressure. I am convinced from repeated observations that a permanent and considerable lowering of blood pressure below what may be termed the standard reading for the case is always associated with, or is very shortly followed by, aggravation of the patient's symptoms, and this is the case whether the fall in blood pressure occurs as a natural event in the course of the illness, or is brought about by the administration of drugs. The effects of digitalis on the blood-pressure reading are not constant, excepting in patients with dropsy who improve under its use; when this symptom sets in the blood pressure falls; as the dropsy disappears the blood pressure rises again to about the height it was before. Under other circumstances the blood pressure sometimes rises, at others falls, but in either case rarely to any extent; and again it may undergo no change with the use of digitalis. In dwelling on these considerations the clinical fact I desire to emphasize is, that fear of ill effects on the pulse or symptoms from a rise of blood pressure is not well founded.

III.

I have had occasion to give digitalis for various reasons to persons with healthy hearts, and out of a number of such cases in which the drug was pushed until its full physiological effect on the stomach was produced, cardiac irregularity, namely, sinus arrhythmia and extra-systoles, ensued in several, but the pulsus alternans occurred in one instance only. The subject of this observation was a female aged 35 years, healthy in all respects except for functional nervous symptoms and a rapid heart. On all the numerous occasions I have examined this person's pulse during the past ten years, it has been regular in force and rhythm under all circumstances, and the usual rate has been about 120 per minute with the body at rest (Fig. 1); under excitement it frequently rises to 150 or 160 per minute, but the exertion of running up and down a flight of thirteen stairs increases the rate only by ten or fifteen beats a minute. There is no evidence of Graves's disease or other condition likely to cause this permanently

frequent pulse, which was uninfluenced in rate by any of the different drugs given from time to time.

For three weeks after the record shown in Fig. 1 was taken, in June, 1910, tincture of digitalis in doses of five minims three times a day was given without change in the rhythm or rate of the pulse. The dose of tincture of digitalis was then increased to fifteen minims three times a day, which was taken until sickness occurred, when the pulse became irregular in rhythm. Over long runs of
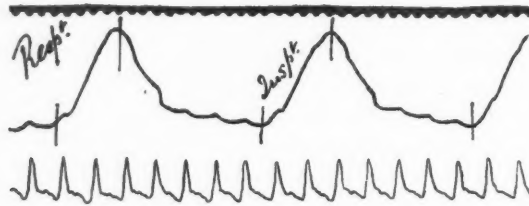
FIG. 1. The record before digitalis. The pulse is regular in rhythm and force; pulse-rate 125 per minute.
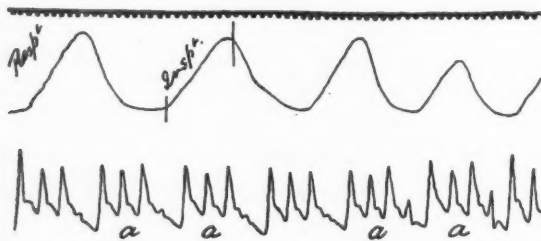
FIG. 2. Record after digitalis. The pulsus alternans succeeds the premature beats; pulse-rate 125.

tracing the allorrhythmia shown in Fig. 2 was present; it is due to an extra-systole, probably arising in the ventricle, recurring after every third normal beat; there is slight but decided pulsus alternans shown in the groups of beats marked a. The circumstances of this observation suggest that the irregularities may be an effect of the digitalis, for before this was given the pulse was always regular in rhythm and force, and has kept so since, and, as stated, there is no evidence of myocardial or valvular disease to explain its presence.

IV.

The pulsus alternans may occur for the first time in patients with heart disease under digitalis treatment, but it is quite exceptional. I have met with but one instance, and in this the pulsus alternans was transient, being present in records taken on one occasion only, and it is difficult to be sure that the drug was its cause. The patient was a boy, aged 13 years, with a very large heart, extensive dropsy, and other symptoms usual in severe heart failure. Up to

July 4, 1910, on which date Fig. 3 was recorded, he had taken five-minim doses of tincture of digitalis four times a day for ten days without change in the pulse or material improvement in the symptoms. From this time the tincture of digitalis was given in fifteen-minim doses four times a day; on July 8 the pulse was slower, and he was much better in all respects. Fig. 3 shows the pulse before the increased dose of digitalis was begun; the pulse-rate is 125 per minute, the more or less periodic rise and fall of the pulse curve is probably due to respiratory changes in blood pressure, since the pulse periods show coincident slight change in duration; but there is no question of pulsus alternans. In Fig. 4, taken on July 8, after about $9\frac{1}{2}$ drachms of tincture of digitalis had been given, the pulse-rate is 93 per minute, and characteristic pulsus alternans is present in the middle portion of the curve; as here shown, alternation was not
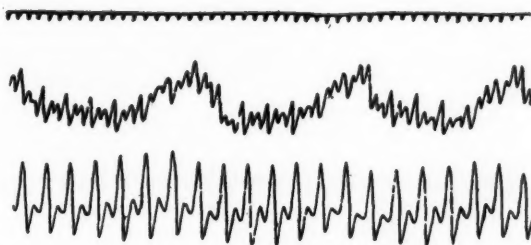
FIG. 3.   After 5 drachms of tincture of digitalis.   Pulse-rate 125 per minute (4/7/10).
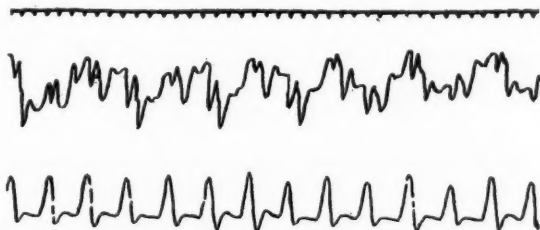
FIG. 4.   After $9\frac{1}{2}$ drachms of tincture of digitalis.   Pulse-rate 93 per minute; the pulsus alternans is present (8/7/10).

continuous, but recurred at irregular intervals in runs of variable length, its onset and offset probably being due to the slight differences in the pulse-rate. For alternation to ensue with slowing of the pulse-rate is exceptional to the rule, and the fact suggests vagal inhibition of contractility as an effect of digitalis may be responsible for the phenomenon; but if this were the case we should expect the pulsus alternans to persist with the further use of the drug. The tincture of digitalis was continued in the same doses until July 12, when sickness ensued; the drug was then stopped. In all the records taken subsequent to Fig. 4 up to July 12 the pulse was quite regular in rhythm and force. On this date the pulse had almost continuously the characters shown in Fig. 5; the radial curve in this tracing bears some likeness to pulsus alternans; most of the beats alternate in strength, but measurement of the pulse periods shows that the

rhythm is not that of the pulsus alternans, since the longer pause follows the weaker beat, and, as already said, the weaker beat in the pulsus alternans never occurs prematurely; the bigeminy shown is probably due to lengthened conduction time for the first beat of the bigeminy, but the venous curve is too indefinite in outline to mark with precision. This patient died from heart failure some three months later, and during this last illness digitalis was freely given, but no alternation in the pulse was recorded at any time.
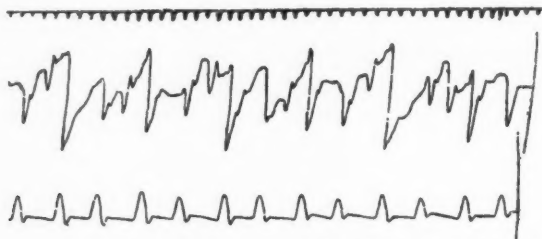
FIG. 5. After 13½ drachms of tincture of digitalis. Pulse-rate 88 per minute; most of the beats stimulate the pulsus alternans.
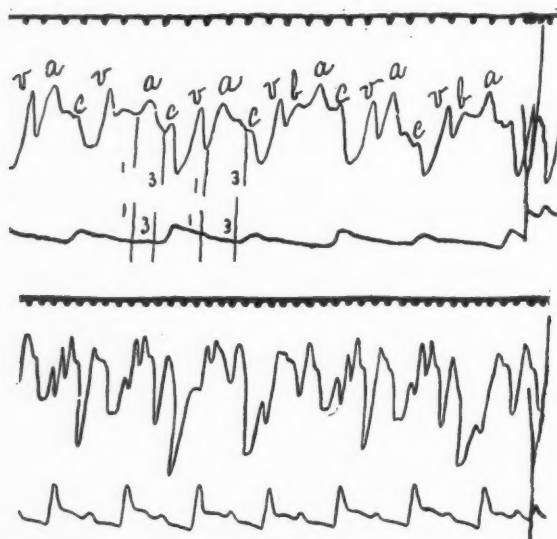
FIGS. 6 and 7. Show alternately strong and weak pulses, due to the sequence of a normal contraction, and one arising prematurely in the ventricle; the pause after the extra-systoles is lengthened. The rhythm ensued after full doses of digitalis.

I have examined records taken from a large number of heart disease patients with a regular pulse under digitalis treatment and in none, except the case last related, is there any evidence of the occurrence of the pulsus alternans. In a number of the tracings, however, a pulse form similar to Fig. 5 is present; in most of these examples the irregularity in rhythm and force is due to an extra-systole succeeding each normal beat. In such cases, when the premature con-

tractions arise in the ventricle the irregularity in rhythm is, as a rule, sufficiently pronounced to be readily recognized by the finger; but if the alternate extra-systoles have their origin in the auricle, the difference in duration of the pulse periods of the normal and premature beats may be so small that it is barely perceptible to touch, and since the premature pulse is usually a feeble one the distinction from the pulsus alternans cannot, as a rule, certainly be made except from a tracing.

Examples are recorded in Figs. 6 and 7, taken from two aged patients with very large hearts and dropsy; the rhythm shown in Fig. 6 ensued on a regular pulse; in the case from which Fig. 7 was obtained pulsus alternans was present. Full doses of digitalis had been taken for some time by both patients; on clinical examination the diagnosis of pulsus alternans was made; in the tracings, however, the feeble pulse is manifestly due to a slightly premature contraction of the auricle occurring alternately to a normal beat.

A pulse rhythm of this kind is not uncommon as an effect of full doses of digitalis, and it is not unlikely that its confusion with the true pulsus alternans explains the ascribed potency of this drug to cause the pulsus alternans.

V.

I have noted the effects of digitalis on the pulse in some thirty cases of heart disease with the pulsus alternans. I have given the drug in varying doses according to circumstances, over weeks at a time, both to patients with rheumatic heart lesions, and to those with degenerative myocardial and arterial disease, and I have never found increase in alternation of the pulse occur which could be ascribed to the drug, or harm result to the patient from its use; on the contrary, the alternation and irregularity in rhythm of the pulse frequently becomes lessened, and not seldom abolished.

There is a close relation between the rate and degree of irregularity in force and rhythm of the pulse and the severity of the symptoms of heart failure; as the character of the pulse improves under digitalis treatment—becoming slower in rate, more regular in strength and rhythm—the patient's symptoms are relieved at the same time; the breathing becomes easier and is not so distressed on exertion, and the symptoms of angina pectoris from which patients with the combination of myocardial and arterial disease with the pulsus alternans so commonly suffer, may for the time cease.

To give digitalis to a patient with degenerated arteries, high blood pressure, and anginal symptoms suggests the probability of dangerous effects, nevertheless it is the only drug which affords some lasting immunity from these attacks to many such patients. Thus Fig. 8 was taken from a working man, aged 66 years, who in spite of the severe breathlessness and paroxysms of angina pectoris from which he had latterly suffered, managed to walk half a mile night and morning to and from his work; on the journey he had ' to stop two or three

times because of a crushing pain in the chest and had to fight for his breath'. The tracing was taken one evening shortly after reaching my house on his way home. The pulse-rate was 100 per minute, markedly alternating in force and irregular in rhythm; the respirations were 32 per minute, and the blood pressure about 180 mm. Hg.

He was not in any club and could not afford to lie up; he was given tincture of digitalis in fifteen-minim doses three times a day. After taking the medicine for a few days his breathing became easy, and by the tenth day of treatment he looked very much better, and so long as he did not hurry was able to walk to and from his work without any distress, which he had not been able to do for weeks before. On this day Fig. 9 was recorded under the same circumstances
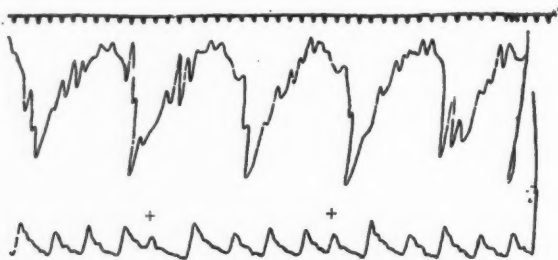
FIG. 8.   Shows a mixture of the pulsus alternans and extra-systoles (marked +). pulse-rate 100; respirations 32 per minute.   Before digitalis.
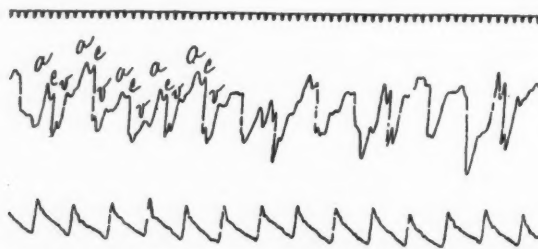
FIG. 9.   From the same case as Fig. 8, after 7 drachms of tincture of digitalis.   A tendency to pulsus alternans is shown; pulse-rate 83; respirations 19 per minute.

as Fig. 8; the pulse-rate was 83 per minute, and the respirations 19; the pulsus alternans was still present, but not so pronounced as before, while the rhythm of the pulse was now constantly regular. The blood pressure was 210 mm. Hg. This case is related to illustrate that digitalis may act well for a time under most unfavourable conditions in a bad case with pulsus alternans. Probably ten days' rest in bed without drugs might have had an equally beneficial effect on the symptoms and pulse, for in most patients who are going about when they first come under treatment the symptoms are usually much improved, and alternation in the pulse becomes less or disappears after a few days in bed. In the later stages, however, and particularly when dropsy sets in, even prolonged rest has often but little influence on the pulse or symptoms; but if now digitalis

is given it frequently happens that within a few days there is a great improvement in the symptoms, the dropsy lessens, and the alternation in the pulse diminishes or disappears.

Thus in the case just related, some weeks subsequently severe dropsy set in and the breathing became so distressed, that he was unable to lie down. No cardiac drugs were given for over a week, and although by this time there was some improvement the dropsy was still present, and the breathing continued troublesome; the pulse-rate was 100 per minute and the beats alternated in strength and were frequently premature (Fig. 10). The day this tracing was taken he was given fifteen minims of tincture of digitalis four times a day, which dose was continued until nausea ensued a week later; by this time the dropsy
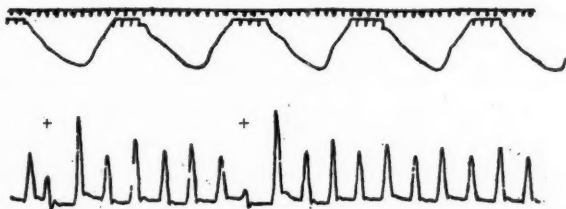
FIG. 10. From the same case as Fig. 8, taken some weeks later, during a break-down with dropsy. Shows the pulsus alternans and extra-systoles (+); pulse-rate 100; respirations 24 per minute.
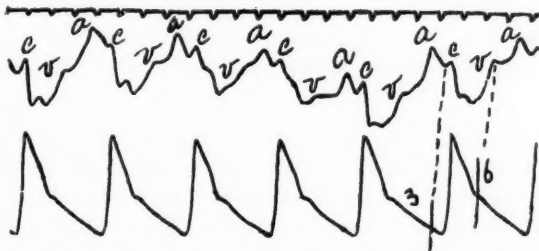
FIG. 11. Recorded a week after Fig. 10. About 7 drachms of tincture of digitalis had been taken; the pulses are equal in strength and rhythm; pulse-rate 79 per minute.

was almost gone, the breathing was easy, and he could lie down in comfort with one pillow. The pulse-rate had fallen to 78 per minute and was quite regular both in force and rhythm (Fig. 11); the blood-pressure reading was not recorded, but there is evidence of a considerable increase in the changed character of the sphygmogram (compare Fig. 10).

I have given digitalis in a number of dropsical cases similar to this with equally good results.

VI.

When dropsy sets in, which it inevitably does sooner or later in all patients with myocardial and arterial disease and the pulsus alternans, the heart enlarges, although rarely to the size it reaches in rheumatic heart disease with equally

severe dropsy ; at the same time the blood pressure falls considerably, but it may be, and usually is, still abnormally high ; the pulse quickens, and often becomes irregular in rhythm for the first time, and together with the quickened rate the degree of alternation is increased ; not seldom, continuous pulsus alternans ensues with the onset of dropsy, when previously brief alternation with exertion or succeeding premature beats only were present.   Under these circumstances I am convinced from repeated trials of different drugs that there is none to take the place of digitalis ; it can be given regardless of the height of the blood pressure or the degree of alternation of the pulse, with confidence in a first attack of dropsy that it will almost surely do good; in such a case great improvement under its use usually occurs in a week to ten days ; by this time the dropsy is much lessened, or may be gone, and the heart is diminished in size and rate, and in proportion to the degree of slowing of the pulse the alternation is lessened, or may be abolished.

In order to obtain these effects a sufficiency of the drug is necessary ; generally speaking, the lower the blood pressure and the more irregular the force and rhythm of the pulse the larger the quantity of digitalis required.   In bad cases fifteen minims four times a day is usually enough, which dose should be continued until the pulse falls to about the normal rate ; if then there is no improvement the drug can be safely pushed until nausea ensues, or the heart takes on a coupled rhythm, which in my experience it does more readily in the pulsus alternans than in any other pulse rhythm except complete irregularity of the pulse.   Vomiting or long runs of coupled heart-beats are indications that the drug should be stopped ; no more good can be expected, and harm may arise from its further use.   The total amount of tincture of digitalis which produces these effects varies in different cases ; in one of my patients vomiting and a continued coupled rhythm of the pulse occurred after three drachms had been taken ; as a rule, however, six to seven drachms is the quantity required.

A brief history of two cases with records of the pulse (Figs. 12–15) will serve for illustration.

The clinical condition of both patients was much alike : they were the subjects of arterial disease with enlargement of the heart ; the pulsus alternans and considerable dropsy of the feet and legs were present.   They happened to be under my care at the same time in 1909, and were the first cases with this combination of symptoms in which I used digitalis.   Various drugs and accessory means of treatment were employed in turn without material improvement before digitalis was resorted to.   The drug was first given in doses of five minims three times a day for ten days, without appreciable benefit but with no ill effects ; the dose was then increased to fifteen minims four times in twenty-four hours.   Within two or three days from this time the breathing became easier and the dropsy less ; about a week later no dropsy was left, and both patients were so much better that they were able to get up ; a fortnight after the increased doses were begun they were able to go about the house comfortably.

Fig. 12 is from one of the cases, a female aged 65 ; it shows the marked
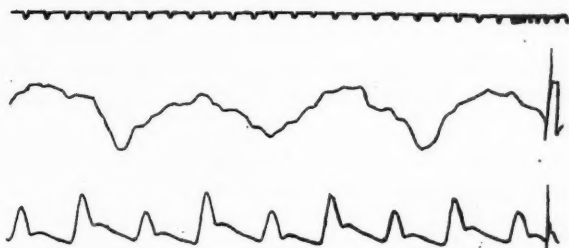
FIG. 12.   From a female patient with cardiac and arterial disease, with dropsy.   Shows the pulsus alternans after 2½ drachms of tincture of digitalis; pulse-rate 105 per minute.
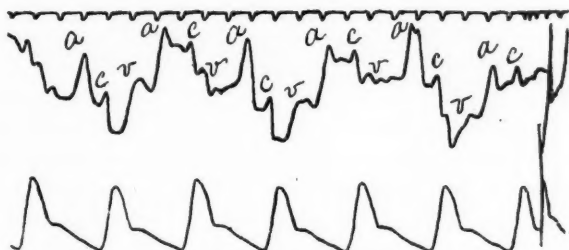
FIG. 13.   Taken from the same case as Fig. 11, after 7 drachms of tincture of digitalis. The pulses are equal in strength ; pulse-rate 82 per minute.
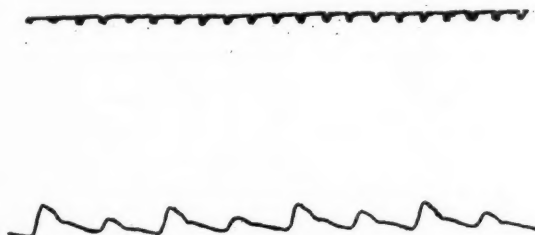
FIG. 14.   From a male patient, with cardiac and arterial disease, with dropsy.   Shows the pulsus alternans after 5-minim doses three times a day of tincture of digitalis had been taken for a week ; pulse-rate 115 per minute.
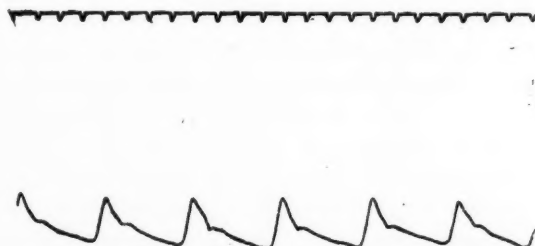
FIG. 15.   From the same case as Fig. 14, after 6 drachms of tincture of digitalis had been taken.   The pulses are equal in strength ; the rate is 79 per minute.

pulsus alternans before the increased dose of digitalis was begun ; the rate of the pulse is 105 per minute, the blood pressure was about 160 mm. Hg.   Fig. 13 is from the same case, after nearly seven drachms of tincture of digitalis had been taken.   The pulse-rate is 82 per minute, and the beats are equal in strength. The blood pressure was 185 mm. Hg.

Figs. 14 and 15 are from the other case mentioned, a male aged 72 years. Fig. 14 shows the pulsus alternans before the larger dose of digitalis was begun ; the rate of the pulse is 115 per minute, the blood pressure was 180 to 185.

Fig. 15 is from the same case after six drachms of tincture of digitalis had been taken ; the pulse-rate is 79 per minute, there is no alternation in strength, the blood pressure was 210 mm. Hg.

It is unnecessary to detail the subsequent history of these cases.   For present purposes it suffices to say that after leaving off the digitalis all the bad symptoms returned within a few weeks, but improvement, as marked as before, followed the further use of the drug in full doses ; relapses, however, ensued again and again in the subsequent course of illness of each patient, and with a view to preventing these relapses, various members of the digitalis series were given in suitable doses over long periods, together with accessory means of treatment ; but in spite of all that was done, the symptoms of heart failure became progressively worse, and ultimately for a long time before the fatal event no drugs had any effect on the symptoms or pulse except morphia.

This epitome of the clinical course applies in general to similar cases : that is to say, in all patients with myocardial and arterial disease with the pulsus alternans and dropsy, the functional cure which usually results under digitalis treatment in the early stages of the illness is temporary only.   Even with pro-longed rest and the greatest care that can be taken in all respects, symptoms of severe heart failure recur.   Digitalis may be, and often is, equally beneficial in a second or even, at times, a third break-down, and I believe the continued use of the drug in suitable doses delays their inevitable occurrence.   In several cases in the late stage, although digitalis preparations have induced a coupled rhythm of the pulse, the dropsy and other symptoms persisted ; generally speaking, however, the drug has no effect on the pulse at this stage.

In the terminal phases of the illness the breathing is always distressed, restlessness is very great, the patient cannot lie down, and sleeps perhaps only for a few minutes at a time.   Morphia is now indispensable ; it quiets the breathing, relieves the subjective symptoms, and maybe induces sleep for three or four hours at a stretch ; the indirect effect of this relief on the heart is often remarkable.

VII.

To illustrate similar changes in pulse strength from digitalis in patients with rheumatic valvular disease with the pulsus alternans, the two following cases are selected.

Fig. 16 is the pulse-tracing from a female patient aged 36 years, the subject of double aortic and mitral valvular disease, of rheumatic origin ; taken on the first day of rest in bed, subsequent to coming under observation. The pulsus alternans is at 125, and the respirations 30 per minute. The heart was greatly enlarged, measuring $1\frac{1}{4}$ inches and $6\frac{1}{4}$ inches in the fourth space to the right and left of the middle line respectively, and the symptoms of heart failure very severe. No active drugs were given for a fortnight ; after a few days the alternation in the pulse was not so continuous or pronounced so long as the patient was at rest, but the exertion of quickly rising in bed and lying down again a few times caused it to become as pronounced as at first ; at the end of the fortnight the pulsus alternans was not manifest at rest, but exertion always brought it on again.
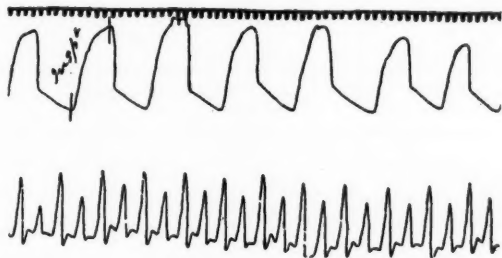
FIG. 16.   From a patient with rheumatic heart disease.   The pulsus alternans is at 125 and the respirations 30 per minute.
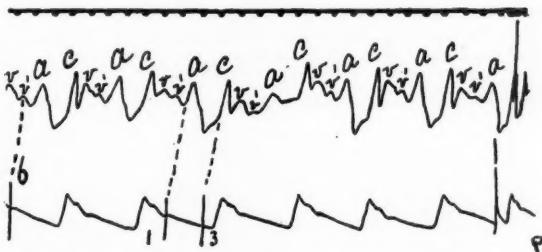
FIG. 17.   From the same case as Fig. 16, after 15 drachms of tincture of digitalis had been taken.   The pulse-rate is 75 per minute.

She was now put on fifteen-minim doses of tincture of digitalis three times a day ; the drug was borne well, and continued for three weeks. Under its use the heart became reduced in size, and the general condition so much improved that she could go quickly up and down a long flight of stairs without much distress ; this amount of exertion quickened the pulse about to the rate it had in Fig. 16, and always induced extra-systoles, which appeared as the pulse began to slow, yet no alternation in strength of the beats was ever present. The tracing after fifteen drachms of tincture of digitalis had been taken is shown in Fig. 17. This patient recovered for a time, sufficiently to resume household work, and the

subsequent month she was under observation the pulsus alternans did not reappear.

The tracings shown in Figs. 18–20 from another case illustrate similar facts. The patient was a woman aged 32 years, with double mitral disease, probably of rheumatic origin. When I first saw her the symptoms of heart failure were extreme; the heart was greatly enlarged; dyspnoea became urgent on the least
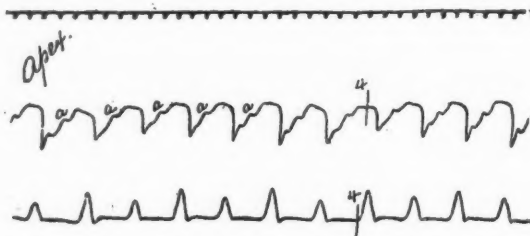
FIG. 18.   From a patient with rheumatic heart disease.   The rate of the pulsus alternans is 93 per minute.   Before digitalis and after three weeks' rest in bed.
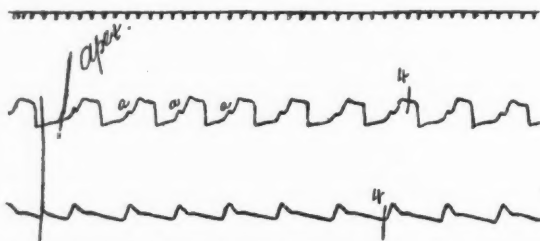
FIG. 19.   Taken from the same case as Fig. 18, a week later, after about 7 drachms of tincture of digitalis had been given.   There is no alternation in the pulse; the rate is 62 per minute.
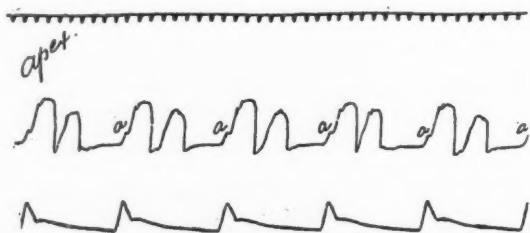
FIG. 20.   From the same case as Fig. 18, after 14 drachms of tincture of digitalis had been taken.   The rate of the pulse is 35, of the ventricle 75 per minute; the half-rhythm of the pulse is due to premature contractions arising in the ventricle too feeble to send the same to the wrist.

movement in bed, and much dropsy was present. She had been in bed three weeks when I first saw her, and because of the presence of pulsus alternans digitalis had been withheld. Fig. 18 is the record taken on this day; the pulsus alternans is at a rate of 93 per minute. She was put on tincture of digitalis, fifteen minims four times a day; within a few days the improvement in her condition was marked, and when I saw her a week later alternation in the pulse

had quite disappeared and she was much better in every way. Fig. 19 was taken on this occasion; the pulse had fallen to 62 per minute, and there was no recurrence of alternation with what exertion the patient was able to make in bed. The digitalis was continued for seven days longer, when the heart had an almost continuous coupled rhythm (Fig. 20), and for this reason the drug was stopped. The half-rhythm of the pulse is manifestly not due to true alternation of the heart, but to alternate premature contractions of the ventricle too feeble to send the wave to the wrist. Exertion caused the pulse rhythm to become regular for a time, but there was no alternation in strength of the pulses; no more digitalis was given to the patient and the pulsus alternans was not again present during the time she was under observation.

VIII.

It is probable the beneficial effects of digitalis in heart disease with the pulsus alternans are largely due to its action in restoring the tonicity of the heart and slowing its rate, although comparison of the tracings taken before and after the use of the drug suggest that it may exert an improving effect on the essential cause which gives rise to the pulsus alternans; that this supposition is improbable is evidenced by the fact that under certain circumstances the alternation is readily reinduced.

IX.

It has already been said that an intimate relation subsists between rate of pulse and the continuance or abolition of alternation in its force, and this association appears, at least in part, to be the explanation of the changes in pulse strength under digitalis; in the figures shown the slowing of pulse-rate in itself is sufficient to account for the cessation of alternation, and all my records from other patients evidence the same fact, namely, that alternation is not replaced by equality in pulse force in cases under digitalis unless at the same time the pulse-rate becomes slower. The rate of pulse at which alternation ceases varies widely in different cases; generally speaking it is unusual for alternation to persist when the pulse falls to about the normal rate, but occasionally it does so, and exceptionally the pulsus alternans continues when the rate is reduced somewhat below the normal.

These relations have prognostic significance, serving to some extent as an index of the functional efficiency of the heart, in so far that alternation expressing disproportion between its strength and rate of contraction, it follows that the slower the rate of a pulsus alternans the greater the exhaustion signified. A slow pulsus alternans, that is to say, about normal rate, is not met with except in cases of senile cardio-vascular degeneration; and it is always of particularly unfavourable prognosis when the pulse-rate falls under digitalis to 70–80 per minute and alternation persists.

X.

In aged patients who once show the pulsus alternans it can be certainly said that it will never again be absent for long; although it may be abolished for a time under digitalis, as the result of slowing of the heart and lessened calls on its strength from restoration of tonicity, yet, if the rate of the heart be again quickened, or it is subjected to additional strain, as for example by exertion sufficient to induce breathlessness, the pulsus alternans is invariably reinduced; moreover, as said, it will inevitably recur in the course of the illness whatever means of treatment are adopted, and however favourable the patient's circumstances may be.

These results are to be expected from the fact first pointed out by Mackenzie, namely, that the combination of arterial disease and the pulsus alternans signifies severe degeneration of the heart muscle; although this may be for a time covert, and the pulse the only evidence of unsoundness of the heart, the condition is permanent and progressive and cannot be cured or retarded by drugs.

In cases of valvular heart disease of rheumatic origin with the pulsus alternans, the circumstances under which alternation in the pulse ensues are different in this respect, that it is never the first manifestation of an unsound heart, as it is in the aged with cardiac and arterial sclerosis; it supervenes only in patients who are already the subjects of severe heart failure, and it signifies not the condition which is the primary cause of the heart failing, but a super-added embarrassment to the circulation. As a rule it first occurs coincidently with increase in dilatation, the onset of dropsy, or other conditions which entail further calls upon the reserve of the heart's strength, which it is unable to meet by full contractions. If the work of the heart is eased, by restoration of its tone, the disappearance of dropsy and so forth, then the pulsus alternans ceases, and may remain absent so long as the factor which was its immediate cause continues in abeyance.

These considerations explain why alternation in the pulse is not usually persistent from the beginning to the end of rheumatic cases, and perhaps also why it is not so readily reinduced after its abolition under digitalis treatment as it is in the degenerative heart lesions of the aged.

XI.

Since this paper was written in 1913, I have continued to use digitalis in heart disease with the pulsus alternans. I have now given the drug to over 100 cases in all, and the results call for no material modification of the statements made in this paper.

CRITICAL REVIEW

THE TREATMENT OF SYPHILIS

By L. W. HARRISON

With Plate 36

FROM the point of view of treatment the history of syphilis may be divided into two periods, the first prior to and the second subsequent to March 3, 1905, the date of Schaudinn's (1) discovery of the Spirochaeta pallida. The division is justifiable since the accurate diagnosis and efficient treatment of the present day owes its being entirely to Schaudinn's discovery.

An inevitable corollary to the discovery of a specific micro-organism is a research into the antibodies to it which are produced by the infected host, and a by-product of such a research in the case of syphilis was the discovery of the Wassermann-Neisser-Bruck reaction (2), to give it its full original name. The argument as to whether the Wassermann reaction is a true Bordet-Gengou phenomenon (3) is beside the purpose of this review. It is sufficient from the point of view of treatment that it complemented the discovery of the Spirochaeta pallida in laying the foundation for exact methods of research into the value of antisyphilitic remedies.

The tripod on which the modern therapy of syphilis mainly rests was completed by Ehrlich's discovery (1909) of dioxy-diamido-arsenobenzol dihydrochloride, known first as '606', or the 'Ehrlich-Hata remedy', and later as 'salvarsan'.

In acknowledging the debt which the modern therapy of syphilis owes to these three discoveries it would be unjust not to mention that Bordet and Gengou (4) had probably seen the Sp. pallida in 1903, and that it was their work on complement fixation which laid the foundation for the Wassermann test. It is also very largely due to the work of Metchnikoff (4) and Roux on the transmission of syphilis to monkeys that the Sp. pallida was accepted so quickly.

THE REMEDIES USED IN THE TREATMENT OF SYPHILIS.

The remedies which are at present employed by different workers for the specific treatment of syphilis are—arsenic, antimony, silver, mercury, iodine, sulphur, and iron compounds. It will be convenient to deal first with each

of these separately and to reserve to the end their proper combination in the treatment of syphilis, taking them in the order named.

The Arsenical Compounds.

As is well known, arsenic had been used empyrically in the treatment of syphilis long before the systematic laboratory researches began which eventually resulted in salvarsan.

The proof by Schaudinn that syphilis is due to a spirochaete at once linked the therapy of syphilis closely to that of other spirochaetoses, and, indirectly, for reasons which need not be detailed, with that of diseases due to trypanosomes. This was a fortunate circumstance, since these diseases can readily be transmitted to lower animals, and experimental research carried out on them with comparative ease.

Uhlenhuth, Gross, and Bickel (5) demonstrated the sterilizing effect of atoxyl on hen spirochaetosis. Levaditi and McIntosh (6) showed that although atoxyl has apparently no effect *in vitro* on the spirilla of hen spirochaetosis, when the mixture is injected into a hen the spirilla fail to infect, and disappear. They concluded from this that atoxyl must act by virtue of a derivative which is split off in the body of the animal. Ehrlich (7) related that he was led to take up atoxyl by the work of Thomas and Breinl, Liverpool School of Tropical Medicine, who (1905) showed that this compound has a destructive effect on trypanosomes in animals. Ehrlich had previously abandoned atoxyl because its effect *in vitro* on trypanosomes was nil, as was shown later by Levaditi and McIntosh in the case of spirochaetes. The conclusion from these experiments that atoxyl must act by virtue of a derivative led Ehrlich, with Bertheim, to investigate again its chemical constitution, with the result that it was found to be not a chemically indifferent anilide, as originally believed, but an amino derivative of phenyl-arsenic acid, namely, para-amino-phenyl-arsenate of soda :

$$\begin{array}{c} \mathrm{OH} \\ \mathrm{As} = \mathrm{O} \\ \mathrm{ONa} \end{array}$$

$$\mathrm{NH_2}$$
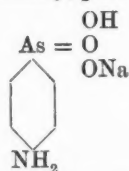
Following on this, Ehrlich sought to vary the constitution of atoxyl, always with the idea of producing a compound with a greater selective affinity for the parasites than for the tissues of the host. Acetylatoxyl or 'arsacetin' was found to be an improvement, as was also the similar compound produced in this country under the name of ' orsudan ',

$$\begin{array}{c} \mathrm{OH} \\ \mathrm{As} = \mathrm{O} \\ \mathrm{ONa} \end{array}$$

$$\mathrm{NH.CO.CH_3}$$
Arsacetin

$$\begin{array}{c} \mathrm{OH} \\ \mathrm{As} = \mathrm{O} \\ \mathrm{ONa} \end{array}$$

$$\mathrm{CH_3}$$
$$\mathrm{NH.CO.CH_3}$$
Orsudan
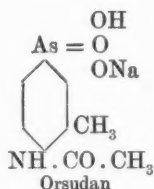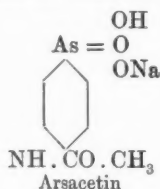
and atoxylate of mercury reported on by Uhlenhuth. In all these compounds the arsenic exists in the pentavalent form. They were extensively tested in syphilis and reported on favourably by many observers. Gradually, however, they acquired an evil reputation and were abandoned on account of the blindness which occasionally followed their use. The first public result of Ehrlich's endeavours to produce a compound in which the arsenic existed in the trivalent form was arsenophenylglycine,

$$\text{As} \quad = \quad \text{As}$$

$$\text{HOOC}.\text{CH}_2.\text{NH} \qquad \text{NH}.\text{CH}_2.\text{COOH}$$

Arsenophenylglycine
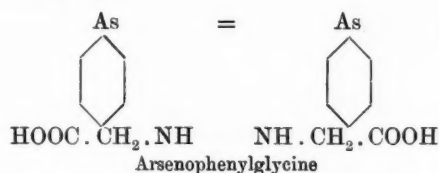
which was reported on by Alt (8) as having a good effect in general paralysis. Arsenophenylglycine has not come into general use, however, as it was quickly superseded by dioxy-diamido-arsenobenzol dihydrochloride or '606',

$$\text{As} \quad = \quad \text{As}$$

$$\text{HClH}_2\text{N} \qquad \qquad \text{NH}_2\text{ClH}$$

$$\text{OH} \qquad \text{'606'} \qquad \text{OH}$$

a canary-yellow powder, which, on account of its liability to change into a poisonous compound on exposure to air, is kept sealed in ampoules in an indifferent atmosphere, such as nitrogen. It contains 34 per cent. of arsenic and forms an acid solution when dissolved in water. The wide margin which exists in spirochaetoses between the curative and the maximum tolerable dose $\frac{\text{DC}}{\text{DT}}$ of '606' is illustrated by the results which Hata (9) obtained in hen spirochaetosis and rabbit syphilis. In the former he found the $\frac{\text{DC}}{\text{DT}}$ to be $\frac{1}{58}$, which compares with $\frac{1}{2}$ for atoxyl, $\frac{1}{3\cdot3}$ for arsacetin, $\frac{1}{2\cdot5}$ for atoxylate of mercury, and $\frac{1}{3\cdot3}$ for arsenophenylglycine. In rabbit syphilis the same ratio for '606' was found to be $\frac{1}{7}$ to $\frac{1}{10}$. At that time the maximum tolerable dose for a rabbit was calculated at 0·1 grm. per kilogram. Present-day preparations of '606' are tolerated by rabbits in doses of 0·12 grm. per kilogram, and the highest dose which is usually administered in one injection to a man is 0·01 grm. per kilogram.

The first report by Alt (10) on the therapeutic effects of '606' on human syphilis aroused such widespread interest that by October, 1910, Ehrlich had complied with requests for 40,000 samples. These were distributed to such hospitals as would be most likely to form a sound judgement on the merits and demerits of the new remedy before it was placed on the market, December, 1910, as 'salvarsan'.

In spite of the fact that salvarsan has not proved to fulfil Ehrlich's ideal of a 'therapia sterilisans magna', and in spite of the opposition which it has met from a small number of workers of great standing in the world of syphilology, it is not too much to say that the arsenical therapy of syphilis, commenced on a scientific basis by the discovery of salvarsan, is now firmly established.   The mountain of literature on the subject which has grown up since March, 1910, precludes any attempt to discuss in detail the views of those who are opposed to the modern arsenical therapy of syphilis.   Most, if not all, of their objections were based on results obtained when the limitations of ' 606 ' were not so well understood as to-day ; when large numbers of patients were injected with unsuitable doses of the remedy, or sent away as cured after one or two injections, to become later victims of severe syphilitic disease of the central nervous system.

The immediate therapeutic effect of ' 606 ' on syphilitic lesions and on the Sp. pallida requires no debate.   Its bitterest opponents must admit that ordinary syphilitic lesions heal up and spirochaetes disappear from them far more rapidly than under the administration of any non-arsenical remedy.

How great a difference Ehrlich's discovery has made in the management of syphilis is shown by these facts : Gibbard and Harrison (11) showed that under systematic mercurial treatment 83 per cent. of soldiers suffering from syphilis required readmission to hospital at least once during the first year for re-appearance of contagious lesions.   In contrast with this, the readmissions for clinical relapse amongst over 10,000 cases of syphilis treated with ' 606 ' and mercury, whose records are accessible to the writer, have been less than 1·3 per per cent.   Under mercurial treatment a soldier spent an average of 66·2 days in hospital during the first year of the disease, while the average time spent by soldiers under ' 606 ' and mercurial treatment at Rochester Row now is twenty-five days.   In this connexion it should be explained that soldiers are kept in hospital for just as long as they exhibit open lesions.   Considering the comparison from the point of view of the Wassermann test, Harrison (12) showed, in an analysis of 492 soldiers whose sera were tested three months after the completion of two years' regular mercurial treatment, that 45·5 per cent. gave a positive reaction to the original test.   In comparison with this, Gennerich (13) found in 162 similar, i. e. primary and secondary, cases who were treated for less than six months with salvarsan and mercury and observed from one to two years afterwards, that 151 remained completely negative to all tests, including examination of the cerebro-spinal fluid after provocative injections.   Of the remaining eleven, four had become re-infected, three had relapsed clinically, two had given a positive Wassermann reaction, and two had remained negative to all ordinary tests but had shown slight changes in the cerebro-spinal fluid after provocative injections.

Shortly after the appearance of salvarsan, a chemically identical preparation was synthesized in France by Billon under the name of 'arsenobenzol (Billon)', and the necessities of the present war have stimulated the production of ' 606 '

in this country under the names of 'kharsivan' and 'arsenobillon', while 'diarsenol' has come from Canada. All these preparations are chemically identical with the original salvarsan, but varying views have been expressed in the literature as to whether they are equal to the original preparation in safety and therapeutic efficacy.

McDonagh (14) related that he had seen six cases of dermatitis and two of jaundice after injections of one of the British preparations, and, from the fact that he also stated he had only once seen such complications under the original, one was led to infer that the new-comer must be inferior. E. Lane (15) also expressed himself very unfavourably regarding kharsivan. On the other hand, Lucey, and also Ffrench, considered kharsivan to be equal in all respects to salvarsan. The writer has had the opportunity of testing salvarsan, kharsivan, arsenobenzol, and arsenobillon during the past two and a half years to the extent of many thousands of doses of each and has been unable to detect any difference between them either in toxicity or in therapeutic efficacy. As to dermatitis and jaundice, these have occurred, if anything, rather more frequently in cases treated with the original salvarsan than with the newer preparations. A study of the literature on salvarsan prior to the war, also, reveals numbers of reports (16) on the incidence of skin disturbance under the original preparation which must convince any one that they are not new nor peculiar to the British and French preparations. One of the worst cases of dermatitis and jaundice which the writer has seen, one which eventually proved fatal, followed on the injection of four doses of 0·3 salvarsan in the course of three weeks. On the other hand, numbers of cases in France and at Rochester Row have been treated with the newer preparations to the extent of 9–16 grm. each without ill effect. As to diarsenol, if one may judge from animal experiments and its effect on a limited number of patients, this is quite equal to the others in all respects. In view of the above, it will be convenient in what follows to refer to salvarsan, kharsivan, arsenobenzol (Billon), and arsenobillon simply as '606'.

Certain difficulties connected with the preparation of '606' for administration led Ehrlich to modify it with a view to obtaining a preparation which would be generally more convenient to prepare for administration. The result was 'neosalvarsan' or '914', a condensation product of formaldehyde sulphoxylate of soda with dioxy-diamido-arsenobenzol,

$$\text{As} = \text{As}$$

$$NH_2 \text{—} \bigcirc \text{—} OH \qquad \bigcirc \text{—} OH \quad NH.CH_2.O.SONa$$
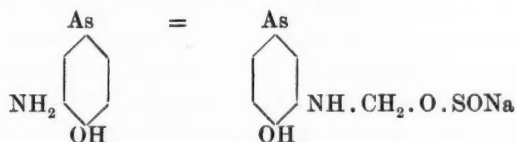
which was first reported on by Schreiber (17). It is a yellow powder which is much more soluble in water, in which it forms a neutral solution; much less irritating to the tissues when injected into them; but much more labile in that on contact with air it rapidly becomes toxic, turning first orange, then reddish, and later, dark brown to black. When injected without delay, it is said to be

less toxic than ' 606 ', but this is a matter of opinion. For purposes of dosage, it is calculated that 0·9 grm. of ' 914 ' is equal to 0·6 grm. of ' 606 '.

The French equivalent of neosalvarsan is novarsenobenzol (Billon), and the British, novarsenobillon. For similar reasons to those mentioned above in connexion with ' 606 ', these products will be referred to below as ' 914 '.

Another preparation, ' salvarsan-natrium ' or ' 1206 ', was introduced by Ehrlich shortly before the war to shorten the steps in the preparation of ' 606 ' for injection. As mentioned, the latter forms an acid solution when dissolved in water or saline, and requires the addition of alkali to make it suitable for intravenous administration. This converts it from

$$
\begin{array}{ccc}
\text{As} = \text{As} & & \text{As} = \text{As} \\
\text{ClH . NH}_2 \overset{}{\underset{\text{OH}}{\bigcirc}} \quad \overset{}{\underset{\text{OH}}{\bigcirc}} \text{NH}_2\text{ClH} & \text{to} & \text{NH}_2 \overset{}{\underset{\text{ONa}}{\bigcirc}} \quad \overset{}{\underset{\text{ONa}}{\bigcirc}} \text{NH}_2
\end{array}
$$
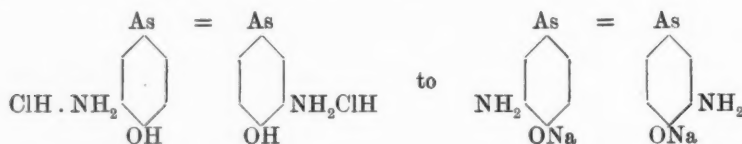
Salvarsan-natrium is the last-named in solid form, and is ready for use on simple solution in water or 0·4 per cent. saline, in which it forms an alkaline solution. The experience at Rochester Row is that it is a very convenient preparation, which seems to cause less reaction after intravenous injection than the others. It is not at present available for general use in this country.

The discussion on two other arsenical preparations of somewhat similar constitution, which have been synthesized in France, ' galyl ' and ' luargol ', may conveniently be deferred until later.

Preparation of ' 606 ' and of ' 914 ' for Administration.

The intramuscular and subcutaneous methods of administering ' 606 ' were quickly abandoned because of the very great pain and necrosis which resulted at the site of the injection, and the uncertainty of absorption of the remedy. Concerning the latter, Beveridge and Walker (18) found 0·029 grm. arsenious acid in 3·7 grm. of a slough removed 111 days after a subcutaneous injection of 0·6 grm. ' 606 ', and Schreiber (17) found one-third of the dose six weeks after an intramuscular injection. Kromayer's suspension in olive oil, Balzer's in lanoline and poppy-seed oil, Schindler's in iodipin and lanoline, and many other oily suspensions certainly relieved the local pain somewhat, but not sufficiently to make this method of administration practicable for general use. In spite of this, the writer has long believed that, dose for dose, the intramuscular and subcutaneous injections of ' 606 ' produced therapeutically better results than the intravenous.

The rectal method of administration has been advocated by Bogrow (19), Plazy (20), and Weil, Morel, and Mouriquand (21), among others, either in the form of solution or as suppositories, chiefly for cases in which it is difficult to perform the intravenous injection, or for any reason the latter method is feared.

C. H. Mills tested this method at Rochester Row and found that three enemata of ' 606 ' (0·6 grm. in each) on successive days failed absolutely to produce any effect on the spirochaetes in the patient's lesions.   Neisser and the vast majority of workers can see no value in the rectal method.

The safety of the intravenous method of administration was first demonstrated by Schreiber (22), and his technique for the preparation of ' 606 ' for administration in this form may form the basis of discussion on the modifications which have since been introduced.   Schreiber's directions were as follows : Dissolve the dose in 10–20 c.c. distilled water, make up to 100 c.c. with distilled water or saline (0·9 per cent.), and add 4 per cent. sodium hydrate solution until the precipitate which first forms is re-dissolved on shaking.   Dilute with 0·9 per cent. saline to a final strength of 0·2 per cent., and administer intravenously without delay.

Very few workers have contested the principle of administering ' 606 ' intravenously in an alkaline form, but Duhot (23) advocated the injection of the acid solution which results from dissolving a dose of 0·6 grm. in 300 c.c. of 0·9 per cent. saline.   Spiethoff (24) holds that, although the immediate reaction which results from intravenous injection of the acid solution is more severe, the therapeutic effect is better.   Hering (25) showed experimentally that acid solutions of ' 606 ' are more toxic to animals, and Joseph (26) that the acid solution forms a precipitate in the blood-stream, which did not occur with alkaline solutions.   Auer (26) found that acid solutions weaker than 0·1 per cent. are well borne by animals.

More workers have sought to increase the concentration of the solution. Altmann and Zimmern (27) tried injection of a 5 per cent. solution of ' 606 ', in place of the 0·2 per cent. advocated by Schreiber, but found that this caused severe pain along the course of the vein and provoked vaso-motor symptoms. Dreyfus (28) found that by injecting slowly with a syringe he could give ' 606 ' in a 1 per cent. solution without exciting more reaction than resulted from injection of the weaker solutions.   He agreed with Zimmern that thus administered it was excreted more slowly than dilute solutions.   Stern (29) found that when concentrated solutions are injected the remedy is excreted much more slowly, and he attributes to this their greater therapeutic effect. An attempt to use solutions which were more concentrated than 0·5 per cent. at the Military Hospital, Rochester Row, was found to cause an increased proportion of vaso-motor symptoms which became more frequent and severe as the concentration was raised.   It may safely be said that the usual practice at present is to inject ' 606 ' intravenously in a final strength of 0·1 grm. in 25–50 c.c.   This does not apply to ' 914 ', as will be shown later.

For reasons which will be discussed later under the heading of toxic effects and their avoidance, it is now usual to use water which has been freshly distilled instead of any distilled water which may happen to be available and may have stood for some days after preparation.   The concentration of the sodium chloride has also been reduced in the practice of most workers to 0·5 or 0·6 per cent.

The preparation of freshly distilled water which is beyond reproach involves
the installation of expensive apparatus and is inconvenient in many ways which
must be obvious.   In order to overcome this, Taege (30) proposed the use of
specially prepared tap-water to which hydrochloric acid was added in such
an amount as when eventually neutralized would produce sodium chloride
solution of the required strength.   Since the presence of the hydrochloric acid
in the water prevented the growth of bacteria, it was not necessary to prepare the
solution on the very day of administration.   A large supply could be made up
at one time and brought into use when required.   The method depends on the
chemical equation :

$$HCl + NaOH = NaCl + H_2O.$$
$$36 \cdot 5 \qquad\qquad 58 \cdot 5$$

Since 36·5 parts of pure HCl produce on neutralization 58·5 parts of NaCl, it is
easy to calculate the amount of HCl which it is necessary to add to the water to
produce eventually the required concentration of saline.   The ' 606 ' is dissolved
in the acid solution, and the neutralization of this and of the added acid is
performed in one operation.

The writer has tested Taege's method extensively, with the slight modifica-
tions that the solutions are freshly prepared, and the acid solution in which the
' 606 ' is first dissolved is weaker than that recommended by Taege.   The result
has shown that Taege's method has many practical advantages over the distilled
water method.   It is not only convenient, but the reactions which follow the
injections are, if anything, less than with ordinary distilled water.   Since, more-
over, the average still cannot be relied upon to produce pure distilled water, and
may, in fact, produce water which is distinctly objectionable, Taege's method
has the advantage that the purity of the water is more under the control of the
worker.

As modified by the writer, the method is as follows :
The heavy earths and metals are precipitated out of the tap-water as
insoluble hydroxides thus : a few drops of a 1 per cent. alcoholic solution of
phenolphthalein are added to the necessary amount of water, say 2 litres, in
a flask, and sodium hydrate solution of any strength which is convenient
(4 per cent.) is added until the formation of a pink colour indicates slight excess
of alkali over that required to precipitate the impurities.   The water is then
boiled for a few minutes and filtered through non-absorbent cotton-wool and
filter-paper arranged in a glass funnel, the filter-paper being next the funnel and
a mass of cotton-wool laid on it.   The filter is supposed to remove the pink
colour, but, as a matter of fact, the filtrate is still slightly pink.   From this
purified tap-water two solutions are prepared :

Solution A, in which the ' 606 ' is primarily dissolved.   To 990 c.c. of the
water are added 10 c.c. of a one in three dilution of dilute hydrochloric acid
(B. P.).   The ' 606 ' dissolves very easily in this solution, and neutralization
eventually requires about 0·5 c.c. more 4 per cent. soda solution than when the
ordinary method is used.

Solution B, for dilution of the alkalized '606' and for general use as 'saline':

Add 10 c.c. strong hydrochloric acid (B. P.) to about half a litre of the purified tap-water. Add sodium hydrate solution of any convenient strength (say 64 per cent.) until the pink colour just returns. Make up to a litre with the purified tap-water.

Knowing that strong hydrochloric acid (B. P.) contains 31·8 per cent. of pure HCl, a calculation based on the above equation will show that the neutralization of 10 c.c. of it with soda will result in just over 5 grm. NaCl, and since this is contained in a litre the required strength of 'saline' has been produced. The final product has a slightly pink tint, owing to its alkalinity and the presence of the phenolphthalein. The detailed steps for preparation of '606' when using the modified Taege's method are as follows:

Pour 50 c.c. of Solution A into a tall, glass-stoppered, mixing cylinder which is graduated, and dissolve in it 0·6 grm. of '606'. When the solution is *quite complete*, and not before, add from a burette 4 per cent. sodium hydrate solution until the precipitate which first forms disappears and a clear solution is left. The amount of soda solution which is required if the above directions are followed is usually about 4·7 c.c. It appears to be an advantage to add 1 c.c. more alkali after the solution is cleared. The solution of alkalized '606' is then diluted to the required strength with Solution B.

The Intravenous Administration of Dilute Solutions of '606'.

The methods employed by different workers vary according to the operators' ideas of convenience. They may be divided into two main classes: (*a*) those in which the remedy is injected into the vein, and (*b*) those in which it flows by gravity. It will be necessary to instance only a few examples of each method.

Schreiber's original method was to inject by means of a syringe, which alternately drew the solution from a glass container and injected it into the vein, a three-way tap being turned as required to direct the stream in the required direction. The syringe is filled with saline, and this is first injected as a pilot in order to make quite sure that the needle is properly in the vein. If it were not, a swelling would in most cases form over the vein, but this would not be of such moment as if the swelling were produced by '606' solution, which is very irritating. The receiving tube is then transferred to the cylinder containing the '606' solution, which is then injected. When the required dose has been administered the receiving tube is again transferred to a cylinder containing saline and one or two syringefuls of saline injected in order to wash the vein wall in the neighbourhood of the puncture free from '606' solution (Fig. 1).

The writer's objection (31) to Schreiber's syringe was to the rigid connexion between the needle and the syringe, which made it difficult in the case of a narrow vein to keep the needle inside the vessel whilst filling and emptying the syringe. This objection was overcome by McDonagh (32), who made the

The preparation of freshly distilled water which is beyond reproach involves the installation of expensive apparatus and is inconvenient in many ways which must be obvious.   In order to overcome this, Taege (30) proposed the use of specially prepared tap-water to which hydrochloric acid was added in such an amount as when eventually neutralized would produce sodium chloride solution of the required strength.   Since the presence of the hydrochloric acid in the water prevented the growth of bacteria, it was not necessary to prepare the solution on the very day of administration.   A large supply could be made up at one time and brought into use when required.   The method depends on the chemical equation :

$$\underset{36\cdot5}{HCl} + NaOH = \underset{58\cdot5}{NaCl} + H_2O.$$

Since 36·5 parts of pure HCl produce on neutralization 58·5 parts of NaCl, it is easy to calculate the amount of HCl which it is necessary to add to the water to produce eventually the required concentration of saline.   The ' 606 ' is dissolved in the acid solution, and the neutralization of this and of the added acid is performed in one operation.

The writer has tested Taege's method extensively, with the slight modifications that the solutions are freshly prepared, and the acid solution in which the ' 606 ' is first dissolved is weaker than that recommended by Taege.   The result has shown that Taege's method has many practical advantages over the distilled water method.   It is not only convenient, but the reactions which follow the injections are, if anything, less than with ordinary distilled water.   Since, moreover, the average still cannot be relied upon to produce pure distilled water, and may, in fact, produce water which is distinctly objectionable, Taege's method has the advantage that the purity of the water is more under the control of the worker.

As modified by the writer, the method is as follows :

The heavy earths and metals are precipitated out of the tap-water as insoluble hydroxides thus : a few drops of a 1 per cent. alcoholic solution of phenolphthalein are added to the necessary amount of water, say 2 litres, in a flask, and sodium hydrate solution of any strength which is convenient (4 per cent.) is added until the formation of a pink colour indicates slight excess of alkali over that required to precipitate the impurities.   The water is then boiled for a few minutes and filtered through non-absorbent cotton-wool and filter-paper arranged in a glass funnel, the filter-paper being next the funnel and a mass of cotton-wool laid on it.   The filter is supposed to remove the pink colour, but, as a matter of fact, the filtrate is still slightly pink.   From this purified tap-water two solutions are prepared :

Solution A, in which the ' 606 ' is primarily dissolved.   To 990 c.c. of the water are added 10 c.c. of a one in three dilution of dilute hydrochloric acid (B. P.).   The ' 606 ' dissolves very easily in this solution, and neutralization eventually requires about 0·5 c.c. more 4 per cent. soda solution than when the ordinary method is used.

Solution B, for dilution of the alkalized '606' and for general use as 'saline':

Add 10 c.c. strong hydrochloric acid (B. P.) to about half a litre of the purified tap-water. Add sodium hydrate solution of any convenient strength (say 64 per cent.) until the pink colour just returns. Make up to a litre with the purified tap-water.

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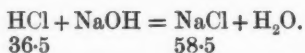### *The Intravenous Administration of Dilute Solutions of '606'.*

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connexion flexible and introduced a special needle which could be strapped to the patient's arm.

McIntosh and Fildes (33) recommended an apparatus which is similar to that illustrated in Fig. 2, and that of Iverson, as well as Bogrow's (34), is on the same principle. As shown in the illustration, the solution is forced into the vein by increasing the pressure of air above it with a pump.
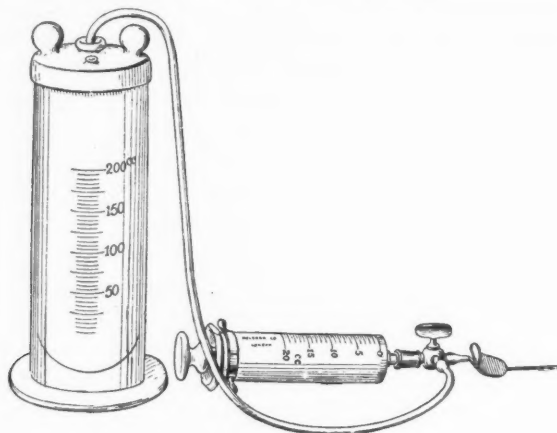
FIG. 1.

FIG. 2.

An objection to the instruments described above is that it is possible with them to force solution into the subcutaneous tissue, should the needle happen to become dislocated from the vein. With a properly arranged gravity apparatus this is impossible. The simplest form of gravity apparatus is one which has been in use for very many years for saline infusion in cases of collapse—a funnel of any pattern from which a rubber tube, provided with a ratchet clip and suitably interrupted by glass windows, leads to a connexion below for attachment of the

needle (Fig. 3). This is first filled with saline to the height of a few inches from the bottom, and air removed from the tubing by this device : The needle connexion end of the tubing is held as high above the level of the saline in the funnel as possible, the clip is opened, and the tubing lowered until a steady flow of saline appears at the outlet. The saline is allowed to flow out of the funnel until its level stands at the bottom of the funnel, when the ' 606 ' solution is poured into the funnel. After the needle has been inserted into the vein and the solution has flowed until it is again about to disappear down the tubing, more saline is poured into the funnel, in order to sweep the remainder of the ' 606 ' out of the tubing and to wash the vein walls. Usually from 10 to 20 c.c. saline is allowed to flow after the last window in the tubing has lost its yellow tint. If the needle
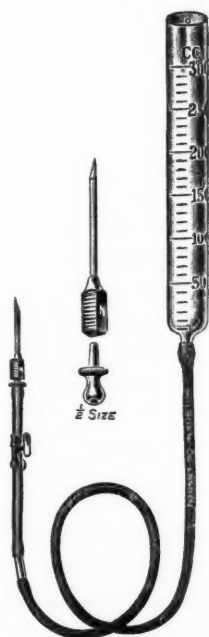
FIG. 3.
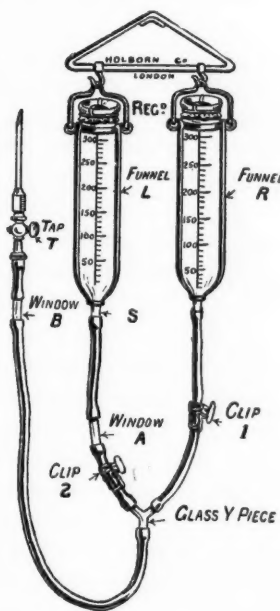
FIG. 4.

is withdrawn too early, before some saline has run through it, there is more likelihood of thrombosis occurring. If the operator is skilled and wishes to save time, it is a good plan before inserting the needle to allow saline to flow until the bottom window just begins to acquire a yellow tint, indicating the arrival of the ' 606 ' at that point. This leaves a few cubic centimetres of saline to act as pilot and ensures that the needle is not covered with ' 606 ' solution at the moment of its insertion.

In order to overcome certain inconveniences connected with the single-funnel apparatus, such as the necessity of standing ready to pour saline into the funnel at the critical moment when the ' 606 ' is about to disappear down the tube, the writer in 1910 suggested the double arrangement, which, after some

slight modifications, has arrived at the pattern illustrated in Fig. 4. It is on the same principle as the single apparatus, but the main portion of the saline is contained in a separate funnel. Before the '606' is poured into its proper funnel—L in the illustration—the whole system is filled with saline by pouring this into one of the funnels and, having opened the clips 1 and 2, allowing it to find its way via the Y-piece into the other. The air is then removed precisely as described in the case of the single apparatus. The saline is then made to flow out of the funnel L (by raising it above the other) until the level stands just at the top of the tube leading out of it, when the clip 2 is closed. After inserting the needle into the vein and opening the tap T behind the needle the level of the saline in the funnel R is watched to ascertain that the flow is satisfactory. The saline is then cut off by closing clip 1, and the '606' turned on by opening clip 2.

The apparatus is a very convenient one for institutional work, since it requires very little attention after the needle has been inserted. A number of sets can be suspended from a horizontal bar, and one operator with three or four attendants can comfortably manage four sets at one time.

A few hints on the technique of veni-puncture may be useful. The vein

FIG. 5.

selected is usually in front of the forearm, close to the bend of the elbow, but on occasion operators have to use other veins, such as one at the back of the hand or the wrist. If the vein has been injected previously it is a wise precaution to palpate it in order to see that it is not thrombosed. The vein is made prominent by fastening a rubber band round the limb on the proximal side of the proposed site of the puncture, in such a manner as to retard the venous but not the arterial flow, and by making the patient clench and unclench his fist a few times, leaving it clenched (Fig. 5). Slapping the arm with the palm of a hand, or with a towel, or steeping it in hot water, are devices adopted at various times to assist distension of the vein. If the vein does not stand out prominently it can generally be felt, unless the patient is too stout, or both stout and muscular. In the latter event it is usually better to make the patient open his hand, since the rigidly contracted muscle behind the vein prevents the latter from being detected by palpation. A needle with a short point is used, since if the point is long it is apt to damage the vein wall more easily and may, moreover, lie partly in and partly outside the vein, allowing some of the solution to trickle into the surrounding tissues. The edges of the bevel at the needle opening should be slightly concave. Some makers produce needles which are ground quite flat here, and they are very trying instruments, since the point of such a needle will not pick up the vein wall. The needle point should be inspected to see that it is not turned.

A very common cause of failure is neglect by the operator to fix the skin over the vein so that skin and vein are, as it were, one. The forefinger of the

operator's left hand should be laid firmly on the skin distally to the site
of the puncture and far enough away from it not to force him to plunge
the needle into the vein at too great an angle. It is an advantage to take
a long hold of the needle (behind the tap in the arrangement shown in Fig. 4),
as too short a hold blunts the sense of touch. The needle is introduced along
the direction of the vein, being held at a slight angle to the plane of the skin,
and with its eye looking upwards. The skin may be punctured directly over the
vein or slightly to one side of its crown. The very common tendency at this
point is to gaze vaguely over the site of the puncture instead of concentrating as
closely as possible on it and picturing by every sense possible the position of the
needle until the latter has entered the vein; this is a very frequent cause of
failure. Another common tendency is to jab the needle through the skin, jab
at the vein, and to end up somewhere, with the needle buried up to its hilt.
A deliberate puncture with a strength of movement which is just sufficient to
carry the needle point through the skin, the faintest possible pause to gauge the
position of the point with relation to the vein, and then a similar, onward push
to carry the point with a few millimetres of the stem into the vein are usually
most successful. If the operator watches the site of the puncture he will usually
see a sign which is of great value. Before the needle enters the vein, while
in fact it is pressing back the anterior wall of the latter, a little dimple appears
in the skin over the needle point. When the latter enters the vein the dimple
flattens out. If the operator is uncertain of having entered the vein he can
verify the fact by disconnecting the needle, when successful puncture will be
demonstrated by a flow of blood from the needle. On remaking the connexion
the needle should be grasped firmly and the connexion made in such a manner
as not to disturb the needle point.

When the needle has entered the vein the necessary tap or clip is opened
and the site watched for swelling, which would indicate that the needle point
had become dislocated. If the latter happened with an infusion apparatus which
was not more than three feet above the patient's arm, the flow of saline would
quickly stop. After the flow has been established it may stop or become
extremely slow. This is usually due to one of three causes. The needle opening
may be pressing against the vein wall; this is rectified by moving the needle
slightly, or rotating it. If this manœuvre does not re-establish the flow the
solution should be cut off, the tubing disconnected from the needle, and the
tourniquet reapplied. If no blood appears the needle is either dislocated or
blocked with clot. In the former event the needle can usually be brought back
again into the vein by moving it intelligently until blood flows. This failing,
another site must be chosen.

It is often taught that the sign of a dislocated needle is the appearance of
a swelling over the vein. This generally does happen, but if the needle point is
in the tissues on the deep side of the vein no swelling may appear. The few
really bad arms resulting from misplaced '606' solution, which the writer has
seen, have been in cases where the operator, relying *only* on this sign of

swelling, which did not appear, assisted the flow by raising the funnel or pumping harder, according to the nature of the apparatus in use. The patient generally feels a burning pain at the site of the injection if the solution is running outside the vein. He may, however, think that this is usual and say nothing about it unless asked.

With a solution of a strength of 0·3 per cent. to 0·4 per cent., a rate of 30 to 40 c.c. per minute (say, four minutes for the administration of 0·3 grm. in 90 c.c. with attendant saline) is usually well borne. If the solution is more concentrated, or if the patient had previously shown signs of vaso-motor disturbance, to be discussed later, it should be given much more slowly.

The Administration of '914'. *Intramuscular and Subcutaneous Injections.*

The objections to this form of administration which were mentioned in the case of '606' do not apply in nearly the same degree to '914'. Even when injected in simple solution it is not followed by nearly the same amount of pain as that which results from the local injection of '606'.

As to local necrosis, Riebes (35) found in animals that just after the injection the muscular bundles were rather separated, and muscles, fibres, and nuclei somewhat shrunken and difficult to stain. After three days only a slight infiltrate was seen, and in eight days numerous connective-tissue cells surrounded the site of injection. As to absorption, he found only an insignificant amount of '914' at the site of the injection after twenty hours. This contrasted with the site of a '606' injection which showed some of the remedy there ten weeks later.

H. F. Swift (36) found more necrosis than this after injection of '914' into the lumbar muscles of rabbits, but the necrosis was not nearly so severe, nor the inflammation surrounding it so intense, as after an injection of '606'. As to absorption, applying the Abelin test for unchanged '606' or '914' to the injected areas, he found that as much had been absorbed from the site of the '914' injection (75 per cent. to 85 per cent. of the dose) after one week as after six weeks following a '606' injection.

The intramuscular or subcutaneous method has not so far become popular. Emery (37), commenting on the adherence of Balzer (38) to the intramuscular method, asks what is the interest in this disused method, which has been abandoned generally on account of its inconvenience and smaller activity.

On the other hand, Wechselmann (39) is a strong advocate of the deep subcutaneous injection of '914' and holds that it is practically painless under a proper technique. He believes that it is much more effective than the intravenous injection of '606', seeing that one gramme of '914' given in this way has often produced in his hands a lasting negative Wassermann reaction, which he has rarely seen achieved by intravenous injection of the same equivalent amount of '606'. He considers the superior therapeutic effect of the subcutaneous method to be due to the slower excretion of the '914' when

administered in this manner. It is interesting in this connexion to recall the fact that methods of intravenous injection which result in slower excretion of the remedy are believed by many to produce better therapeutic results.

Harrison, White, and Mills (40) found in two parallel series of similar cases treated with equivalent amounts of ' 606 ' intravenously and '914' intra-muscularly or subcutaneously, that the negative Wassermann reactions at the end of the course were 12 per cent. better after the intramuscular or subcutaneous injection than after the intravenous, as shown in Table I.

TABLE I.

Showing the Wassermann Reaction after the Injection of 2·8 grm. Salvarsan Intravenously and after the Subcutaneous Injection of 4·2 grm. Neo-salvarsan, or Less, respectively.

Stage of Disease.	Method.	No. of Cases.	Wassermann Reactions at End of Course.							
			Actual.				Percentages.			
			+	±	±	−	+	±	±	−
Primary	Subcutaneous	67	0	0	3	64	0	0	4·4	95·5
	Intravenous	79	3	6	4	66	3·7	7·5	5·0	83·5
Secondary	Subcutaneous	76	11	4	7	54	14·4	5·2	9·2	71·0
	Intravenous	141	35	16	8	82	24·8	11·3	5·6	58·1
Tertiary	Subcutaneous	18	10	3	1	4	55·5	16·6	5·5	22·2
	Intravenous	31	18	1	3	9	58·0	3·2	9·6	29·0

Interpretation of symbols : + = positive reaction ; ± = doubtful reaction, nearer positive than negative; ± = doubtful reaction, nearer negative than positive ; − = negative reaction.

Notes.— 22 received 4·2 grm. neosalvarsan (equivalent to 2·8 grm. salvarsan) ; 40 received 4·05 grm. neosalvarsan (equivalent to 2·7 grm. salvarsan) ; 99 received 3·9 grm. neosalvarsan (equivalent to 2·6 grm. salvarsan). All cases in each series received one weekly injection of mercury grm. 1.

The Technique of Subcutaneous and Intramuscular Injections of '914'.

Wechselmann and Eicke (loc. cit.) recommend that the solution be placed on the fascia covering the glutei, on account of the comparative freedom from pain and of the better absorption of the remedy which results from choice of this site. The dose (0·1 to 0·45 grm.) is dissolved in 1 c.c. saline; the needle is inserted over the glutei in such a manner that its point lies in the loose tissue immediately overlying the fascia. This is ascertained by two signs : (i) on rotating the needle the skin does not twist with it, and (ii) when some saline is injected through the needle (which is one with a rather wide bore) it returns freely through the latter. In practising this method, the correct position of the needle can be ascertained by scraping its point over the fascia, which

communicates a characteristically harsh feeling to the operator's hand. Or by pushing the needle right through the fascia at a slope and withdrawing it again whilst levering the point outwards; as the needle leaves the fascia a characteristic click is felt. Major C. F. White (private communication), on an experience of 9,000 subcutaneous and intramuscular injections, prefers the former.

Balzer and Beauxais-Lagrave (41) have experimented with various solutions and oily suspensions for intramuscular injection and, so far, have found the following to be the best:

Novarsenobenzol	0·2 grm.
Guaiacol crystal	0·2 grm.
Stovaine	0·01 grm.
Solution of glucose (chemically pure) 180 per cent. to 1 c.c.	

The guaiacol and stovaine are anaesthetic and antiseptic, while the glucose, being a reducing substance, is calculated to prevent oxidation of the ' 914 '. The authors maintain that the preparation is stable. After twelve to twenty-four hours it sets to a thick mass, which becomes fluid again on gentle warming. It is claimed for this method that the pain which results from the injection is negligible and has disappeared after two hours. If it persists it can be relieved by hot fomentations and the administration of pyramidon or of aspirin. A dose of 0·25 grm. is administered to men twice a week into the gluteal or the lumbar muscles, and fifteen to sixteen injections are given in one course.

Harrison, White, and Mills (loc. cit.) have tried both these methods. They found that after the deep subcutaneous injections of 0·6 grm. the injection was tolerable, but apt to be followed by tender swellings over the site. As above mentioned, White now prefers the subcutaneous method, since it does not leave any stiffness of the muscles. The dose employed was greater than that recommended by Wechselmann, and this, no doubt, accounts for the discomfort having been greater than that recorded by the latter.

The mixture of Balzer and Beauxais-Lagrave was found to be stable within the limits of the observation period (about three weeks), and well borne in the doses recommended by these workers; but a higher dose, which was aimed at in order to reduce the number of injections necessary, caused sufficient discomfort to stimulate further efforts at improvement of the mixture. After trying various combinations, one in which the solution was emulsified with a creosote-camphor cream base, or with camphophenique, was found to have given the best results up to date. The details of technique at present practised at Rochester Row, which were not given in the original paper, are as follows :

Technique.

1. Take a record syringe, remove the piston, and cap the nozzle with, say, the base of a hollow needle with the stem hole made up, or a metal cap made for the purpose.

2. Pour 10 minims of distilled water into the syringe and dissolve the '914' in it with the help of a glass rod. In doing so, hold the syringe vertically and pour the powder into the water in such a manner that none touches the sides.

3. Make up to 2 c.c. with the melted creosote-camphor cream base (formula 4631, B. W. & Co., melting at 15° C.).

4. Refit the piston, removing the cap temporarily whilst doing so.

5. Replace the cap when the piston is half-way up the barrel and shake well.

6. Insert the needle first into the gluteus medius, as for intramuscular injections of mercury—upper and outer quadrant of the gluteal region. Push the needle in until its point touches the iliac bone, then withdraw it about two millimetres.

7. See that no blood is oozing from the needle base.

8. Holding the needle in order that the position of its point may not be disturbed, fit the syringe to it and inject *slowly*. If the patient complains of pain running down the leg, withdraw the needle and select another site.

9. Before removal, rotate the needle once or twice on its long axis, and as it is being withdrawn, pinch up the skin and subcutaneous tissues around the needle as if to wipe the latter dry with skin and subcutaneous tissues.

10. Hold the skin and subcutaneous tissues thus for a few seconds after the needle has been withdrawn.

11. Give a hypodermic injection of morphia, gr. $\frac{1}{8}-\frac{1}{4}$, into another site.

12. Massage the site of the '914' injection with a large pad of cotton-wool the size of a tennis ball sewn up in lint, so as to dissipate the dose.

At the present moment this technique has succeeded in very largely abolishing immediate pain, and the great majority of patients make no complaint whatever. Three or four days later, however, a local reaction commences which makes the gluteal region stiff and rather tender for a few days. Patients of sedentary habit seem to suffer more, since soldiers on full training duties do not ask for 'excused duty' or 'light duty'. Patients naturally vary greatly with regard to local reaction and pain, and it is difficult to convey by description an accurate impression of it. The practice at Rochester Row is to give seven injections at weekly intervals, and it is rarely that the course has to be interrupted on account of local reaction, while in some cases thirteen or fourteen injections have been given without interruption. Complaints as to discomfort have been encouraged by careful inquiry, in full knowledge of the fact that an enthusiast is notoriously apt to be blind to the disadvantages of his pet method, but very few patients have requested a change to intravenous treatment. The writer is fully conscious that the method is not yet perfect, but the

encouragement to persevere with its improvement lies in the fact that while it is not followed by any vaso-motor disturbance and the technique is so simple that it can be practised anywhere, the therapeutic results are better than those which follow the intravenous method.

The Intravenous Injection of ' 914 '.

When first introduced '914' was dissolved for intravenous injection in about 100 c.c. distilled water or 0·4 per cent. saline at room temperature and given in much the same manner as '606' is injected now. But since Ravaut (42) and Duhot (43) independently advocated the injection of this remedy in concentrated solution, the latter method has generally been adopted.

It has the advantages of simplicity and probably greater safety, since a shorter time intervenes between the opening of the ampoule and the injection of the remedy, while the latter is brought less into contact with such disturbing elements as water impurities, which will demand considerable attention below.

The writer has used boiled tap-water (10 c.c. for the solution of 0·9 grm. of '914'), as recommended by Stern (44) and by Katzenstein (45), with impunity in some thousands of injections.

Alexandrescu (46) gives a solution which is still more concentrated. He dissolves 0·9 grm. of '914' in 1 to 2 c.c. of distilled water in the ampoule itself. This is also the practice of Strauss (47) and of numerous medical officers in the French Army (48).

The technique of administration of concentrated solutions is simple. The dose may be dissolved in the syringe itself or in a small gallipot, using either distilled or boiled tap-water. It is wise to fit a short pointed needle to the syringe for the same reasons as were mentioned in the case of '606'. When the needle has entered the vein blood is seen to flow back into the syringe, especially if the piston of the latter is gently pulled upon. The injection can usually be completed in one minute from commencing to press the piston home, but in some cases it may be advisable to inject much more slowly, as in the case of '606'.

The Fate of ' 606 ' and '914' after Injection.

Abelin (49) by testing for the amido group of '606' found that it continues to circulate in the blood *as such* for about one and a half hours.

Riebes (50), applying the same test, found that in practically all cases '606' could not be detected *as such* in the blood after three hours. In the urine it was found from a few minutes to about twelve hours after the injection, the great majority of the sixty-five cases tested failing to give the amido reaction after nine hours. The effect of repeated injections was interesting in that patients who received three injections of small doses in two days were those who gave the reaction in the blood serum later than four hours after the last injection. One patient, who gave a salvarsan reaction in the blood as long as

nineteen hours after the injection, died three days later. The vomit gave the reaction once only in seven cases. In this case the '606' did not appear in the urine for three hours, and this was the only patient who displayed symptoms of vaso-motor disturbance.

McIntosh and Fildes (51) found that after injecting a rabbit with 0·15 grm. '914' per kilogram the blood was practically free from *arsenic* two days later. The dose here was proportionately to weight about ten times as much as that used by Riebes on patients.

Swift and Ellis (52), experimenting on the effect of the blood serum on spirochaetes, found that one hour after injection the serum had a damaging effect, but that this had disappeared after six to twenty-four hours, by which time the serum had also become therapeutically less active. They found also that heating the serum increased its antispirochaetal and therapeutical power. The time during which these authors found active spirochaeticidal properties in the blood agrees closely with that found by Abelin and by Riebes as the period during which '606' circulates as such in the blood. It differs considerably from the findings of Stühmer (below), but the latter injected proportionately to weight at least seven times as large a dose.

Swift (53) estimates that one hour after an intravenous injection of '606' the blood contains 0·01 mg. per c.c., and 10 to 20 c.c. serum would then contain 0·1 to 0·2 mg. of '606', which is the amount he recommends for intraspinal injection.

Stühmer (54), experimenting on rabbits, found that after the injection of 0·075 grm. '606' per kilogram, or about seven times as much proportionately as is given to man, he could detect evidence of '606' or an active derivative of it up to seven days after injection. Thus, when samples of serum were tested for their protective power against trypanosome infection of a mouse, it was found that serum drawn off three days after injection, heated at 56° C. for forty minutes, and mixed with blood containing active trypanosomes prevented infection by the latter when the mixture was injected after five minutes' contact. Serum which was drawn off seven days after the injection and similarly treated postponed but did not prevent eventual infection. Chemically, the blood serum gave the Ehrlich-Bertheim reaction for '606' for as long as it gave any protection. Serum which was not heated was much less powerful, protecting only up to twenty-four hours and postponing infection when drawn off not later than two days after the injection; similarly, unheated serum gave a weaker Ehrlich-Bertheim reaction. He concludes that since 1 c.c. of a 1 in 800 solution of '606' (0·00125 grm.) would have been required to afford the same protection, and since it was impossible for this quantity to have been present in the 0·5 c.c. of rabbit serum which was used, the latter must have derived its antispirochaetal power from some derivative of '606'. He found that the serum lost its protective power much more rapidly after intravenous injection of '914', the effect having disappeared after two days.

The excretion of arsenic after '606' and '914' injections has been worked

out by numerous workers, whose results substantially agree. After intravenous injection of '606' the greater part of the arsenic has disappeared from the urine and faeces in from ten to fifteen days, though traces may be found for months. It is interesting in connexion with the delayed commencement of excretion reported by Reibes (above) that Bar (55) reported a case in which no arsenic was found in the urine for the first twenty-four hours, and this patient developed hemiplegia and convulsions, and died comatose on the third day after injection.

As mentioned, Stern and others found that after '606' had been injected intravenously in concentrated solution it was excreted much more slowly.

The excretion of arsenic appears to be much more rapid after intravenous injection of '914'; thus Hudelo (56) found that most of it had disappeared in eight hours, and practically none could be found after two days.

All workers agree as to the very irregular and slow excretion of arsenic after intramuscular injections of '606', but this does not apply to '914' administered in the same way, the excretion of arsenic under this method approximating closely to that which follows the intravenous injection of '606'.

Fraenkel-Heiden and Navassart (57) found that the bowels excrete from two to ten times as much of the arsenic as the kidneys.

Arsenic is found in the organs for months after the injection of both remedies; thus Stumpke and Siegfried found evidence of its presence in spleen, heart, lungs, kidneys, and especially in the liver, for months afterwards.

Ritter (58) found arsenic in the liver of a rabbit up to thirty days after an injection of 0·01 grm. '606' per kilogram. When two injections had been given at an interval of eight days arsenic was found up to seventy days later, and after three similar injections in sixteen days it was found a hundred days later. This illustrates the slower excretion of the remedy and its cumulative effect which result from repeated injections.

Practically all workers agree that while arsenic may be found in all organs, except the brain, after injection of '606' and '914', the greatest amounts are generally found in the liver. As to the brain, opinion is almost unanimous that neither '606' nor '914' reaches the parenchyma of this organ unless it is injected intrathecally.

McIntosh and Fildes (51) conducted an elaborate research into this question in the case of rabbits which had been injected with '914', and found that, although brain tissue will combine in vitro with this remedy, as well as when the latter is injected intrathecally, none could be found in the brain even after repeated injections, except once when 0·0001 grm. of '914' was found in 10 grm. of brain twelve hours after the last of eight injections of 0·05 grm. '914' which had been given in four days. This agrees substantially with the results obtained by Ullmann (59), who found arsenic in the brain extremely seldom, and then only in quantities which could not be estimated. Riebes (loc. cit.) found minute traces of arsenic in the brain once in twenty-six cases. The records as to the finding of arsenic in the brain of patients who have died as the result

of '606' and '914' injections are almost unanimously negative, and the conclusion is that when injected intravenously or intramuscularly these remedies must reach the parenchyma of the central nervous system only very exceptionally in quantities which are chemically detectable.

The Effect of '606' and '914' on the Tissues.

Practically all are agreed that the injection of these remedies is followed by a fall in the blood pressure. Thus, Hedén (60) found the pressure reduced for two to three days after an injection, while controls treated with saline showed no fall. Auer (61) showed a fall of blood pressure in a rabbit after injection of '606' and believed that this was due to the effect of the drug on the heart. Rolleston (62) found that both the diastolic and systolic pressure fell after injections of '914', though both were raised during the actual injection, especially if this was the first. He does not consider that the fall in blood pressure is due to the direct action of the remedy, but that rest in bed is a factor. The rise during injection is the result of the excitement.

Hedén (loc. cit.) found a moderate leucocytosis after injections of '606', and this has been confirmed by many observers. Hudelo (56) found after injections of '914' a moderate, but inconstant, leucocytosis (8,000 to 14,000 per c.mm.), and a diminution of red blood cells (by about 200,000 to 1,000,000 per c.mm.). This also has been noted by various workers.

Milian (63) considers that a vaso-dilator action is exercised, and that the serous exudation into the tissues which results from this accounts for many of the side effects to be mentioned later.

Numerous workers have investigated histologically the tissues of men and animals after death from poisoning by the newer arsenical remedies. Most are agreed that the changes found are the result of poisoning by these remedies, and not by endotoxins of spirochaetes killed by them, as was claimed at first.

Marschalkó and Veszprémi (64) investigated carefully the tissues of a patient who died a few days after an injection of '606'. The chief changes were found in the brain, which showed numerous punctiform haemorrhages, around which the brain substance was somewhat oedematous. A similar haemorrhage, the size of a poppy seed, was found in the left endocardium. Otherwise, except for considerable congestion, the other organs presented to naked-eye examination nothing particularly abnormal.

Histological examination of the haemorrhagic areas in the brain showed the capillaries to be blocked with hyaline thrombi, in which no red cells were visible, while in other vessels, some of them larger, the thrombi were attached to the vessel wall, partly blocking it. In addition to this, the larger capillaries and some of the other vessels showed such a degree of stasis that the red cells were collected into large masses in which the individual corpuscles could not be recognized. The extravasation of red blood cells had taken place from the

capillaries, in some places completely filling the perivascular lymph spaces and in others extending into the neighbouring brain tissue. The condition of stasis, with filling of the capillaries with hyaline thrombi, was found also in some places which had appeared normal to the naked eye. There were no signs of previous disease, and the authors, having produced similar changes in rabbits which they had poisoned with the remedy, concluded that the changes found were due to poisoning with '606'. They considered that '606' by its damaging action on capillary endothelium causes spastic contraction of the vessels, leading to thrombosis and transudation of blood cells from the blocked vessel.

Other workers have found similar changes in the kidneys. Busse and Merian (65) found minute haemorrhages in the kidneys, with cloudy degeneration and extensive shedding of the epithelium of the convoluted tubules, many of which showed only shadows of epithelium. Similar changes were found in the glomeruli. Stühmer (66), reporting on the kidney changes in two cases of death following an injection of '914', found that these were similar to those produced by mercury—vascular nephritis, with necrosis and calcification of the epithelium of the straight and convoluted tubules. Having produced the same effects by injections of hydraldite and sodium hydrosulphite (substances which are used in the manufacture of '914' and of '606'), as well as by injection of laked blood cells, &c., he holds that the toxic effect is the result of the presence in the blood of reducing substances, and not of arsenic.

Greff (67) found in rabbits which were killed with 0·1 grm. '606' per kilogram tubular nephritis, with necrosis and calcification of tubules in certain parts. Pearce and Brown (68) conducted an exhaustive research into the effect of various arsenical preparations on the kidneys and suprarenal capsules. They found that, while arsacetin produces a tubular nephritis and the effect of arsenious acid is on the vessels, that of '606' and '914', as well as galyl, is generally a combination of the two. There was considerable necrosis of the cortical tubules, which was most marked in the inner half, while congestion and haemorrhages, though general, were especially marked in the outer half of the cortex. On the suprarenal glands toxic doses produced congestion, haemorrhages, and disturbance in the lipoid content. This may be a factor of importance in the production of side effects.

The kidney changes recorded above have been confirmed by Gennerich (69) and many others in fatal cases.

Ricker and Knape (70) concluded as a result of observations on the mesenteric vessels of animals that '606' and '914' may cause blood stasis and capillary haemorrhages when the vessels are exposed to abnormal irritation, even though the effects of such irritation may not have been noticeable in the vessel immediately before the arrival of the arsenical preparation.

Viktor Caesar (71), discussing the causation of cerebro-disturbances, came to the conclusion that the primary effect is on the capillaries. He quoted the finding of Schmorl, who could discover no thrombosis, but a generalized fatty

degeneration of the capillary endothelium, even in places where there was no haemorrhage.

Wechselmann (72) holds that '606' acts primarily on the vessels of the kidneys. If these had been damaged indirectly by the previous administration of mercury, which causes at first a tubular nephritis leading later to disease of the vessels, the latter are less able to withstand the effects of the arsenical preparation. The first dose in such cases may not produce any appreciable results, but a second may cause complete loss of ability to excrete the '606' which is retained in the blood. Here it acts as a reducer, removing the oxygen from the blood cells and producing a form of internal suffocation which is manifested by the intense cyanosis, convulsions, and coma, which are seen in fatal cases. In this connexion the observation of Riebes, mentioned above, as to the finding of '606' in the blood of fatal cases long after it should have disappeared is interesting, and it is quite possible that a diminution in the amount of urine excreted after injections of these arsenical preparations may be a warning sign that the remedy has had a more profound effect on the kidney vessels than is usual.

The writer has had the opportunity at various times of examining the organs of cases which have died after injections of '606', death having been the result of convulsions in one case, and of the complications of dermatitis in others. In the case where the patient had died in convulsions only the brain and kidney sections were available. The former showed no particular abnormality, but in the kidney were found changes similar to those described above. In the fatal cases which followed on dermatitis a histological examination was possible only once, and here were found haemorrhages into the lung alveoli, with stripping of the epithelium of the duodenum. (For the preparation of and the reports on these specimens the writer is indebted to Dr. J. A. Murray, of the Imperial Cancer Research, acting on behalf of the Medical Research Committee.) In this, as in other cases, a noticeable feature was the large number of submucous petechiae and small ecchymoses which were seen macroscopically in the large and small intestines, and the purpuric spots found scattered over the skin during life. Similar haemorrhages into the lungs have been observed by the writer in rabbits which have been killed with '606'.

A tentative conclusion from the observations recorded above would appear to be that '606' and '914' exercise their toxic effects chiefly on the capillaries and vessels generally, and that the nature of the manifestations which develop as a result of this depends on the topography of the affected vessels. If these are situated in the brain, capillary haemorrhages appear there; if in the kidneys, a vascular nephritis is produced, and it is possible that dermatitis is the result of damage to the capillaries of the skin. It is possible that, as found experimentally by Ricker and Knape above, an abnormal condition of the capillaries in one situation or another determines the organ or tissue in which the toxic effect becomes manifest. Thus, it is a frequent observation at Rochester Row that patients who are naturally prone to dermatoses are more likely to suffer from

erythemata and dermatitis under injections of '606' than others. Possibly an early stage of the process is a wide dilatation of the vessels followed by serous exudation, which may proceed to minute blood extravasations. This would explain all the stages from simple vaso-motor disturbance to epileptiform convulsions on the one hand, or to dermatitis on the other.

The cumulative effect of these remedies is agreed upon by all writers. This is seen clinically in the fact that patients who have shown the most severe toxic effects have in the majority of instances done so after a number of doses had been administered. For the most part the intervals between doses have been very short, but in a number of cases they have been sufficiently long to allow of a large proportion of the preceding dose being excreted, and it is possible in these cases that each succeeding dose contributed its quota to the damage, which was finally precipitated by a fresh dose. The following experiment may illustrate the point. Incidentally it throws a little light on the varying experiences of different clinics as regards the occurrence of late toxic effects, although all may appear to be similar in regard to the incidence of immediate reactions. Some '606' of a particularly good batch was prepared for administration by two different methods, A and B, which, though differing slightly, are in fairly common use at the present moment. Three rabbits were injected intravenously with 0·08, 0·10, and 0·12 grm. respectively per kilogram, prepared by Method A, and three others of approximately equal weight were injected with similar doses prepared by Method B. All six rabbits survived. The following day each of the first three received a further dose of 0·08 grm. per kilogram prepared according to Method A, and the second three a similar dose prepared by Method B. The first three rabbits died the same night. One of the second three died ten days later and post-mortem showed no particular evidence of '606' poisoning. The other two rabbits were killed off after three weeks.

Clinical Side Effects, their Prophylaxis and Treatment.

The literature on the side effects which may result from the administration of the newer arsenical compounds is uniform as to the nature of the symptoms which may be encountered, but the opinions as to the aetiology of these are somewhat conflicting. Before discussing this, it may be well to detail the symptoms which may be displayed after injections of '606' and '914', apart from the therapeutic effects of these remedies.

In roughly chronological order they are as follows.

Occurring during, or immediately after the injection :

(i) Vaso-motor disturbances, also known as anaphylactoid symptoms, or minor nitritoid crises.

(ii) Syncope.

(iii) Pain in the gums and teeth.

(iv) Peculiar taste in the mouth.

Following the injection usually by a few hours, and occurring generally on the same day:

(v) Rigor, rise of temperature, headache.

(vi) Vomiting, diarrhoea, pain in the back, and cramp in the legs.

(vii) Urticaria, herpes (labialis and zoster).

At various times from a day or two to a month or longer after a single injection or a course of such:

(viii) Albuminuria.

(ix) Stomatitis.

(x) Chronic headache, lassitude, loss of appetite, weight, and sleep.

(xi) Erythema and dermatitis.

(xii) Jaundice.

(xiii) Severe cerebral symptoms.

To consider the above rather formidable list in detail:

(1) *The vaso-motor symptoms*, which have also been designated by different authors as anaphylactoid or as nitritoid crises, vary somewhat in degree and occur only after intravenous injections. They are commoner after injections of ' 606 ' than ' 914 ', and the most usual symptom is puffing of the face, dilatation of the pupils, rapid pulse, feeling of constriction about the mouth and throat, and perhaps some precordial distress with coughing. In a more severe degree the face becomes intensely congested, the lips and tongue may swell considerably, the precordial and respiratory distress is great, and there may be some convulsive twitching of the limbs. If the symptoms commence after the patient has left the table and before he has got to bed, he may lose consciousness, or this may occur on the table. Sometimes immediately after an attack the body is covered with urticaria. Usually all symptoms have passed off in about half an hour, but exceptionally they may persist for several hours. As to their frequency, it is difficult to form an estimate, since some patients are particularly susceptible, being affected with every dose they receive, and one such case increases the percentage incidence in a hospital considerably. Again, there is no doubt that different batches of the remedy vary in their power of promoting these vaso-motor effects and the use of a disturbing batch for some time increases the incidence in that clinic. On an average, one would judge the proportion all the year round to be rather less than 1 per cent. of injections. Lloyd Jones and Gibson (73), dividing the above symptoms into cardiac, respiratory, and cerebral, according to the predominance of signs, found that the incidence under each category was 0·53 per cent. of injections. Milian's experience of the treatment of 532 cases showed that twenty-six of these, or 4·88 per cent., suffered from these symptoms during the course of their treatment.

As to their causation, on account of their similarity to those of anaphylaxis or of serum sickness, various authors have attributed the above symptoms to this cause, but this view has not received much support. Stühmer (66) considered that the effect of ' 606 ' and of ' 914 ' on the blood was sometimes to produce a foreign albumin, the repeated introduction of which into the circulation

had the same effect in producing serum sickness as the injection of a foreign serum such as horse serum. He considered the symptoms, in fact, to be due to auto-anaphylaxis.

Against this view Brauer (74) showed that the injection of the serum of affected patients into animals does not produce a passive anaphylaxis. He considers that the symptoms are vaso-motor in origin. Auer (75) failed to produce any anaphylaxis in animals by suitably spaced injections of ' 606 ', such as would occur under injection of a foreign serum.

Milian (63), as mentioned above, attributes the symptoms to serous exudation following on great vaso-dilation. If this occurs in the brain a form of serous apoplexy results, giving rise to cerebral symptoms of greater or less severity which may not be manifest for a few days, as in the cases where the patient develops convulsions. A milder degree of the same cerebral vascular dilation would cause more or less severe headache. Owing to the similarity of the symptoms to those produced by amyl nitrite, he named the symptoms nitritoid crises and recommended for their treatment the intramuscular injection of $1\frac{1}{2}$ to 2 c.c. of a 1 in 1,000 solution of adrenalin hydrochloride. The exhibition of this remedy has often been found efficacious at Rochester Row, both therapeutically and prophylactically, the latter in cases which have previously been affected. Often a smaller dose, say 10 to 15 mm. of adrenalin, injected immediately prior to the administration has prevented the symptoms from appearing in a patient who has previously suffered from them.

(2) *Syncope.* It is a fairly common event for a patient to become faint during the injection. In the majority of instances the cause is mental, and in the remainder it is usually found that the patient has indulged in a meal immediately before the injection. In the latter case the symptoms are the prelude to an attack of vomiting.

(3) *Pain in the gums and teeth* has been noticed by various authors and attributed by some to destruction of spirochaetes in the decayed socket, since it probably occurs more frequently in patients suffering from stomatitis. It is unlikely that this is the explanation, since the exhibition of these remedies through the blood-stream appears to have little effect on the number of spirochaetes which are found in cases of pyorrhoea. It is much more likely that the symptoms are vaso-motor in origin, and that the added congestion of the gums produced by dilatation of the vessels there is the cause of the pain. If this is correct, pain in the gums, &c., could be regarded as a minor form of the symptoms mentioned under (1).

(4) *A taste of garlic, or of ether or chloroform,* during the injection was considered by Milian (loc. cit.) to be a minor sign of intolerance. It occurs most frequently when concentrated injections are being given, and does not appeal to the writer as a sign of any importance.

(5) *Urticaria* during or immediately after the injection is comparatively rare, but when it does occur then it usually succeeds a severe vaso-motor reaction. It is rather more common as a later event.

(6) *Rigor, rise of temperature, and headache* are amongst the commonest

sequelae of arsenical injections. The symptoms usually appear within two hours and have generally disappeared by the following morning. Rigor and headache are usually so slight that the patient would not mention them unless questioned; the rise of temperature is exceptionally to 104° F. or even 105° F., but in the vast majority of cases it does not reach 101° F. In frequency these symptoms vary very greatly with the type of case, and practically all agree that with modern technique they are by far the most frequently found after first injections, especially in cases of generalized syphilis.

Lucey (148) found that rigor occurred in 5 per cent., and headache in 17 per cent. of his cases. Lloyd Jones and Gibson (loc. cit.) found that rigor occurred in 9·9 per cent., and headache in 27·3 per cent. of the 1,320 injections on which they reported. The experience at Rochester Row is illustrated in Table II, which shows the enormous preponderance of these symptoms after first injections as compared with later.

(7) *Diarrhoea and vomiting* are much less, and are usually very slight, the diarrhoea being limited to two or three loose motions, and the vomiting to little more than retching. Very occasionally, one or both may be very severe and accompanied by pain in the back and cramps in the legs. It usually happens in these cases that a number of patients are affected on one day, and investigation then discloses some error in technique. As to their incidence Lucey (loc. cit.) found vomiting, usually slight, but occasionally severe, to be 7 per cent., and diarrhoea, varying from two to eight motions in twenty-four hours, 10 per cent. Lloyd Jones and Gibson reported vomiting some time after injection in 15·3 per cent., and diarrhoea amounting to two or three loose stools in 24 hours, 29·3 per cent. Tables II and III show the experience at Rochester Row regarding the symptoms mentioned under (6) and (7), and it will be noted that, like rigor, fever, &c., diarrhoea and vomiting are also more prevalent after first injections.

(8) *Herpes labialis and, occasionally, herpes zoster* are very infrequent. Sometimes they appear very closely on the heels of severe attacks of vomiting and diarrhoea, and in the experience of the writer they have been more frequent at times when some error in technique has resulted in a short outburst of severe reactions such as are mentioned under (6) and (7).

(9) *Albuminuria* is not common after injections of '606' and '914'. Rarely it is accompanied by casts. More often albuminuria precedes the first injection and disappears afterwards. Appearing for the first time after the injection it is naturally an indication for caution as to succeeding doses. Another indication for caution is marked diminution in the quantity of the urine passed in twenty-four hours, as already mentioned.

(10) *Stomatitis.* Except for the pain in the gums at the time of injection, stomatitis has apparently not been attributed in the literature to the arsenical preparation. This is probably because most workers treat syphilis by the combined arsenical and mercurial method, and any stomatitis which may occur is attributed to the mercury. It is the strong impression of the writer, however, that patients on combined mercurial and arsenical treatment suffer more frequently from stomatitis than those under purely mercurial or arsenical. Probably

TABLE II.

Reactions after 1st, 2nd, 3rd, and 4th Injections respectively of '606' and '914'.

After	No. of Injections	Temperatures							Headaches.				Diarrhoea.				Vomiting.			
		100°–101°	101°–102°	102°–103°	103°–104°	104° and over.	Total over 100°.	%	Slight.	Severe.	Total.	%	Slight.	Severe.	Total.	%	Slight.	Severe.	Total.	%
1st Injection	803	92	91	77	52	16	328	40·9	228	74	302	36·3	139	27	166	20·6	80	24	104	12·9
2nd Injection	767	48	7	5	5	1	66	8·6	74	22	96	12·5	57	6	63	8·2	13	2	15	1·9
3rd Injection	614	16	18	6	6	—	46	7·4	61	19	80	13·0	35	6	41	6·5	12	8	20	3·2
4th or later	110	6	4	1	—	—	11	10	16	2	18	16·2	12	3	15	13·6	9	2	11	10
Totals	2,294	162	120	89	63	17	451	19·6	379	117	496	21·1	243	42	285	12·4	114	36	150	6·5

TABLE III.

Reactions after different Doses of '606' and '914'.

(Separate Series from that shown in Table II.)

After		No. of Injections.	Temperatures.		Headache.				Diarrhoea.				Vomiting.			
			Total over 100°.	%	Slight.	Severe.	Total.	%	Slight.	Severe.	Total.	%	Slight.	Severe.	Total.	%
0·3 grm. '606'	{ Salv.	149	52	34·9	18	19	37	24·8	3	1	4	2·6	8	4	12	8·0
	{ Khar.	349	89	25·5	29	48	77	22·0	3	1	4	1·1	10	6	16	4·5
0·4 grm. '606'	{ Salv.	49	10	20·4	2	6	8	16·3	1	1	2	4·0	4	1	5	10·2
	{ Khar.	62	12	19·3	3	4	7	11·3	3	—	3	4·8	3	4	7	11·3
0·5 grm. '606'	{ Salv.	73	17	23·3	10	4	14	19·2	1	3	4	5·4	14	1	15	20·5
	{ Khar.	144	23	15·5	13	10	23	15·9	4	—	4	2·7	8	9	17	11·8
0·45 – 0·6 grm. '914'		602	29	4·8	55	50	105	17·4	10	1	11	1·8	29	13	42	6·9

Salv. = salvarsan.   Khar. = kharsivan.

'606' given intravenously; '914', intramuscularly or subcutaneously.

the latter may not be nearly so active in causing stomatitis, but adds sufficiently to the irritation produced by the mercury to precipitate a stomatitis which would not otherwise occur.

(11) *Chronic headache, lassitude, loss of appetite, general malaise, insomnia, and loss of weight* are symptoms which are occasionally displayed during the later parts of a course of injections. They are considered by Milian to be signs of intolerance to the arsenical preparation and indications for caution regarding succeeding doses. In the opinion of the writer they are signs, the observance of which will often prevent the onset of more severe symptoms, such as dermatitis, jaundice, and cerebral symptoms.

(12) *Dermatoses* in the form of urticaria have already been mentioned. Some patients complain of itching of some particular part of the body after each injection, and this may be a sign of intolerance. A patient in the care of the writer suffered from severe pruritis ani after each injection of '606', and six weeks after the completion of the course had a single epileptiform convulsion from which he recovered easily. His cerebro-spinal fluid was normal in every respect, and the convulsion was attributed to '606'. Patients occasionally display, and that after a number of injections have been administered, an erythema which may be punctate or morbilliform. It may be limited to a small portion of the body and disappear in a few days, or may spread all over the body, and then usually develops into severe exfoliative dermatitis. In the latter event, which is fortunately rare, the body is covered with a scarlatiniform erythema, and the face becomes considerably swollen. Numerous blisters or pustules form, and the breaking of these leads to crusts and scabs, especially at the fissures. The condition is accompanied by most extensive exfoliation of the epidermis, and there is considerable pruritus. The skin assumes a deep red-brown tint, and after scaling the patient looks generally as if he had been boiled. The skin remains in a semi-atrophic condition for many weeks after the acuter symptoms have passed away, and considerable pigmentation results. The constitutional symptoms may be slight, even in cases of severe dermatitis, but in these the health naturally suffers from the loss of sleep and other causes incidental to the discomfort which the skin condition entails. In other cases there is considerable rise of temperature, and this may be accompanied by diarrhoea; the tongue becomes dry and brown, and the patient passes into a condition of toxaemia which is very similar to that seen in typhoid fever. It is common in severe cases to find petechiae in the skin after the dermatitis has progressed for some time. Broncho-pneumonia is another serious complication of dermatitis and particularly fatal. The general nutrition suffers severely in most cases and recovery is a matter of many months. As to the incidence of dermatitis, little information is available from the literature. Brauer (76) stated that dermatoses occurred in 1 per cent. of cases. Lucey in the course of 600 injections saw a limited erythema in one case. Lloyd Jones and Gibson in the course of 1,320 injections experienced one severe case of dermatitis, which recovered. In a hospital which was formerly under the control of the writer the incidence of dermatoses of all kinds in the course of

80,000 injections to about 10,000 patients has been 26 severe, 24 moderately severe, and 74 classified as mild or trivial, including limited urticaria, or a total of 124 cases of all kinds. There were eight deaths as a consequence of the complications which occurred in certain of the cases. In six of these cases there was a greater or less degree of broncho-pneumonia, and in two the symptoms simulated more closely those of typhoid fever. In three of the five cases of which a moderately detailed report of the post-mortem examination is available a noticeable feature was the presence of a number of small submucous ecchymoses in the large and small bowel. These varied in number from about ten patches, each about the size of the finger-nail, to innumerable linear ecchymoses throughout the small intestine. The number of injections which these cases had received before the outbreak of the dermatitis was 4, 5, 6, 8, 8, 8, 8, and 8 respectively, the dose in each case being 0·3 grm. The symptoms commenced 3, 3, 6, 7, 9, 11, and 28 days afterwards in seven of the cases, while the particulars on this point in the eighth case are not available at the moment of writing.

Table IV, for which the writer is indebted to Major C. F. White, R.A.M.C., shows the number of injections of 0·3 grm. '606' which preceded the dermatoses mentioned above. The table shows that more than half the severe cases had received seven or more injections, and more than half the mild ones, three or less. Naturally, treatment was stopped, or continued very cautiously, after the slightest sign of skin trouble, so that the fact of a patient's skin remaining tolerant throughout the greater part of a course of injections is no guarantee that the attack will be a mild one.

The treatment of dermatitis may conveniently be considered later with that of other side effects.

(13) *Jaundice* is much less frequent than dermatitis. In the experience of the writer it has occurred in about 0·6 per cent. of cases which have received a number of injections (Table V). The symptoms were those of the ordinary obstructive type, which is very persistent. In a case seen by the writer where the patient had suffered also from dermatitis and had died, the liver showed no particular degenerative changes, but there was obstruction of the common duct at its entrance into the duodenum, which was inflamed.

(14) *Severe cerebral symptoms characterized by intense headache*, followed by mental confusion, epileptiform convulsions, coma, and in a large proportion of cases death, have been recorded by a number of writers. They are the symptoms which precede death in the very great majority of fatal cases. They have become much less frequent in later years, probably owing to the greater caution which is now exercised as to initial doses and care over the purity of solutions than prevailed in the earlier years of modern arsenical therapy. Leredde (77) quotes the following, in illustration of this point, from the thesis of Jamin:

Year.	Number of Injections.	Deaths of all Kinds.
1910	50,000	16
1911	800,000	92
1912	1,200,000	66
1913	2,000,000	37

TABLE IV. *Showing the Incidence of Dermatoses of all Kinds in 10,000 Cases under '606' and Mercurial Treatment and the Number of Preceding Injections (of 0·3 grm.).*

Degree of Severity.		Number of Preceding Injections of '606'.															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Severe	No. of cases	—	—	6	2	4	—	3	7	—	1	—	—	1	1	—	1
Moderately severe	No. of cases	—	4	10	3	2	2	1	2	—	—	—	—	—	—	—	—
Mild or trivial including urticaria	No. of cases	2	10	27	7	6	1	9	9	1	—	1	1	—	—	—	—
Total		2	14	43	12	12	3	13	18	1	1	1	1	1	1	—	1

TABLE V. *Similar to Table IV but showing Incidence of Jaundice.*

Degree of Severity.		Number of Preceding Injections.							
		1	2	3	4	5	6	7	8
Severe	No. of cases	—	—	4	1	—	3	—	2
Moderately severe	No. of cases	—	2	4	—	2	3	2	3
Mild	No. of cases	—	—	4	1	7	2	1	1
Total		—	2	12	2	9	8	3	6

Possibly the smaller incidence of reported fatalities in the later years is partly accounted for by the fact that cases have not been reported so freely since their novelty has worn off, and since, perhaps, they have been attributed so often to errors in technique. A real diminution in the number of fatalities is shown, however, by the following facts. Ravaut (48), reporting on French army medical experience, records no death, but two cases of epileptiform convulsions (one neosalvarsan and one galyl) and one case of transient coma (neosalvarsan) in the course of 94,762 injections. The writer has not seen a fatal case of epileptiform convulsions, but has received reports of three deaths (kharsivan) which have occurred in an estimated total of about 140,000 injections. In addition to this, two patients under the care of the writer had each a single epileptiform convulsion six weeks after completion of a course of treatment, but recovered without apparent after-effect.

The sequence of events in fatal cases, as usually described, is as follows: Within a period which ranges in the great majority of cases from twenty-four to 120 hours after the injection, there is a complaint of intense headache with mental confusion, which is quickly followed by a series of epileptiform convulsions; the patient becomes extremely cyanosed, comatose, with marked Kernig and Babinski signs, incontinence of urine and faeces, and rise of temperature (to perhaps 108° F.), and dies within twenty-four hours of the onset of the symptoms. In some cases there is complete suppression of urine, in others it is scanty and full of albumin, and in still others no particular changes have been noted in this respect. Sometimes there is a temporary pause in the symptoms, which generally return, however, and the patient dies some days after the onset (78). In milder cases a few epileptiform convulsions are followed by unconsciousness for a number of hours, and the patient then recovers. In others the cerebral symptoms have manifested themselves by temporary loss of memory, which has lasted sometimes for as long as two weeks. As Milian remarks, between the vaso-motor reactions noted under (1) and the severest of the symptoms under discussion, there may be all varieties of cerebral disturbance.

The main post-mortem appearances which have been recorded in these cases have already been discussed (p. 311).

The Aetiology of Side Effects.

The factors concerned in the above side effects may be considered from the points of view of susceptibility of the patient and of toxicity of the remedy.

The varying susceptibility of patients to the toxic effects of ' 606 ' and ' 914 ' must be clear to any one who has witnessed the behaviour of many hundreds of patients injected under identical conditions, and is evident, too, from the proportionate incidence which has been mentioned under each heading in discussing the above side effects. It is generally recognized that, even excluding cases in which there is indication for caution in regard to dosage, it is impossible

to tell by examination of an apparently healthy patient before he receives an injection whether or not he will be tolerant of the remedies. It is for this reason that the majority of authors recommend a cautious start in regard to dosage, and that a close watch be kept on the patient for signs of intolerance as the course of treatment proceeds.

Milian (79) drew up a list of signs of intolerance, most of which have been mentioned already but are worthy of closer review, since it often happens that lack of attention to the minor signs results later in the development of grave symptoms. He divided the signs of intolerance into mild and grave, thus : *Mild signs.*—An odour or a taste of garlic, &c.; hypersecretion of certain glands, especially the lachrymal; increased intestinal secretion, causing diarrhoea; possibly increased secretion of the choroid plexus, causing severe headache; vaso-motor symptoms or 'nitritoid crises', such as congestion of the face, swelling of the lips, &c., as described above, during the injection; slowing of the pulse, when this is not due to the injection being given too rapidly; prolongation of rigor, fever, and vomiting, especially the latter, into the next day, or undue intensity of these; repetition of the immediate reaction after the second or third injections in a form as severe as happened after the first; prolongation of the reaction so that the patient remains in bed longer than usual, suffering from great malaise, feeling of fatigue, and tendency to vomiting and diarrhoea on slight provocation, with insomnia for two or three nights after the injection; rise of temperature on the third or fourth day after the injection; buzzing in the ears; pruritus, often with punctate erythema or urticaria; pains in the joints, especially in the back, and persistent congestion of the face and eyes, with subicterus coming on after the second or third day. *Grave signs.*— Persistent vomiting, scarlatiniform erythema, jaundice, and the graver forms of vaso-motor disturbance,—'crises nitritoïdes secondaires'.

Practically all these signs have been discussed, and there is no doubt that attention to the milder ones will often prevent the onset of the graver. The writer has often noticed in cases of severe dermatitis that the patient, after experiencing the usual tonic effect of the remedy during a portion of the course, had gradually begun to suffer from indefinite malaise and had unfortunately not mentioned the fact. It is true that many cases of severe dermatitis have felt remarkably well throughout the course, but the high proportion of cases of dermatitis which have shown minor signs of intolerance during the course makes these of considerable value. A few cases of dermatitis have shown a mild and transient erythema earlier in the course, which should have been a warning to proceed with extreme caution.

The susceptibility may be increased artificially. It has generally been found that patients who have fasted for some hours prior to the injection, and have taken a laxative the night before, have suffered much less from reaction than those who neglected these precautions. Milian (80) believes that the preceding diet should be arranged so as to render the blood strong in basic substances in order that the injected remedy may not disturb the reaction

of the blood. For this reason he recommends restriction of meat, acid salads, and fruit, and the giving of milk and vegetables. Westrope (81) claimed that by putting the patient on a milk diet for twenty-four hours previously he had very considerably reduced the number and severity of reactions. Whereas formerly all his patients had suffered from headache and vomiting after the injections, the introduction of the change in diet produced the following results. In a hundred cases, seventy-seven remained quite free from symptoms; of the remaining twenty-three, nineteen vomited and nine of these suffered also from diarrhoea, while three of the remaining four suffered from diarrhoea and one from albuminuria.

It is generally considered, too, that exertion or the taking of food soon after injection increases the susceptibility to the remedy. The clinical evidence on this point is not very convincing. That severe exertion or the taking of food may make a reaction apparent which was previously latent is comprehensible, because a patient who worked hard afterwards would naturally feel worse under the same toxic effect than one who laid in bed, just as one who ate solid food immediately after injection would vomit more easily than one who fasted, but this does not prove that the tissues are more poisoned thereby. In this connexion, however, the experiments of Auer (82) to demonstrate the effect of ' 606 ' on the heart are interesting. He found that in certain animals the heart was thrown into a state of fibrillation after injections of ' 606 ' in alkaline solution. He believes, since this did not occur with the same proportionate dose in every animal, that when it did occur the remedy had precipitated the condition in a heart which suffered from some inherent weakness. He found in this the experimental support to Ehrlich's warning not to administer his remedies to cases of myocarditis, or to do so only with great caution. In the same connexion it is conceivable that a patient who exerted his heart unduly soon after an injection might put it under a disadvantage with regard to its power of withstanding the toxic effect of the arsenical preparation, which would then cause fatal fibrillation.

Alcoholics are generally more susceptible, if one may judge from the case-records of deaths. Probably this is due to the toxic effect being exercised on blood-vessels which are already diseased, especially the kidney vessels. Possibly, too, the perverted metabolism of an alcoholic favours more rapid decomposition of the remedy within the organs and tissues.

Mercury is believed by Loewy and Wechselmann (72) to increase susceptibility to ' 606 ' and ' 914 '. They found that animals which had been treated previously with mercury died of smaller doses than controls, and hold that the mercury renders the vessels more susceptible to the toxic effect of the arsenical preparation.

Pregnancy is a condition in which there is reason to feel anxiety regarding the kidney functions, and probably for this reason Gennerich (83), otherwise a supporter of the combined treatment, would withhold mercury from women who are pregnant.

With regard to dermatitis, the writer has found that this is much more severe in cold than warm weather. For example, courses of 2·4 grm. '606' each were administered to about 2,500 cases during ten months, chiefly in summer, with the occurrence of a trifling number of cases of dermatitis, none of which caused any anxiety. In the succeeding five winter months, the patients being, too, under canvas in an exposed situation, a number of severe cases of dermatitis occurred, and amongst them the deaths which have been mentioned above. During the succeeding summer dermatitis was also seen, but there were no fatal cases, and it is probable that the care which had been taken to keep patients warm whilst undergoing treatment with '606', &c., has been to a large extent responsible for the immunity from fatalities which has been enjoyed by the hospital concerned during the past fifteen months.

Another factor connected with the state of the patient with regard to susceptibility to reaction concerns not the toxic action of the arsenical preparation on his tissues, but possibly the effect of the former on the spirochaetes infesting them. Either by release of endotoxins from killed spirochaetes or as a result of temporarily increased ante-mortem activity of the spirochaetes, the remedy may exercise an indirect toxic effect on the tissues. This has been held in some quarters to account for practically all the side effects which have been recorded above.

It is generally accepted that the administration of an antisyphilitic remedy, whether mercurial or arsenical, to a person suffering from syphilis may result in a transitory exacerbation of all symptoms. The phenomenon is known as the Jarisch-Herxheimer reaction, and can easily be observed in syphilitic skin and mucous membrane lesions on the day of the first injection of '606' or '914', or on that following it. It is a fairly common event to see increased redness and swelling round a primary sore on the following day, as remarked very early by Queyrat and Boutier (84). Intensification of the rash and shortly afterwards increase in the strength of the Wassermann reaction are other manifestations of this reaction. The increase in the strength of the reaction or the production of a positive reaction in a patient who was previously negative by the injection of a small dose of '606' or '914' is now put to practical use in determining the question of cure, and in deciding sometimes as to the syphilitic nature of obscure cases where the Wassermann reaction is negative or doubtful. The injection of the remedy is known as a 'provocative' injection, and following on it the blood is tested at intervals of a few days, as suggested by Milian (85).

As to the effect of the Jarisch-Herxheimer reaction on the central nervous system, the cases collected by Ehrlich (86) are very interesting. Thus Beck, Biehl, Simchovicz, and Mongrovius reported on four cases of paralysis of the auditory nerve which came on from a few hours to ten days after injection. Makroki recorded a case of paralysis of the oculo-motor nerve two days after, and Claude, one of facial paralysis three days after an injection of '606'. These early cranial nerve disturbances were attributed by Ehrlich to increase of reaction in a syphilitic infiltration of the meninges around the nerve in question,

just as is seen so often in visible syphilitic lesions. They should be distinguished carefully from those later disturbances known as neuro-recurrences, which occasionally come on some weeks after cessation of anti-syphilitic treatment and, as will be shown later, are relapses of the syphilitic process around these nerves. Probably most will agree with Ehrlich's view as to the causation of the early cranial nerve disturbances occurring within a few days of the first arsenical injection; that they are, in fact, manifestations of a Jarisch-Herxheimer reaction there. Few, however, will now go so far as Ehrlich did at one time in attributing most of the deaths in epileptiform convulsions to this cause. The argument on this account is that in these cases the sudden release of spirochaetal endotoxins in the meninges caused profound general irritation of the brain. As Marschalkó and Veszprémi (loc. cit.) have pointed out, many similar cases of death have been recorded in cases where the meninges have not been particularly invaded by the spirochaetes. Most of the deaths, also, have been after the second or a subsequent injection, and a Jarisch-Herxheimer reaction is seen only after the first injection. Further, the reports on many of these cases showed that the cerebro-spinal fluid prior to death was apparently normal, a fact which is incompatible with the supposition that the meninges were profoundly infected by the parasite. One must conclude with Tomaczewski (87) and many others that a Jarisch-Herxheimer reaction will not explain any but a minute fraction of the severe disturbances which have been recorded after arsenical injections.

It is possible, however, that rigor, fever, and headache depend largely on release of endotoxins, if one may judge from the fact that, as shown in Table II, irrespective of the dose employed, these symptoms are by far the most frequent in occurrence after the first injection administered to cases of late primary or early secondary syphilis. Further, when, as advocated by Touton (88), Schreiber (89), Gennerich (90), and others, a mercurial course precedes the first arsenical injection no reaction occurs, or at any rate the frequency is reduced to that of cases in much later and much earlier stages of the disease.

The Factors concerned in Increasing Toxicity.

Water impurities. Since Wechselmann (91) first pointed out that reactions were much more frequent and severe after injections or arsenical remedies which had been prepared with stale saline and distilled water, than when solution was effected in freshly distilled water and saline made from such, considerable research has been carried out to determine the part which water impurities play in the causation of reactions. While practically all observers now agree that the use of freshly distilled water has effected a very considerable reduction in the severity and frequency of the reactions observed in the early days, opinions are divided as to whether water impurities are the sole cause of these disturbances.

Some observers have considered the matter from the point of view of toxicity of the saline itself rather than from that of interaction between the water impurities and the arsenical preparation. Wechselmann (loc. cit.) held that the reaction was due to insufficient sterilization of the water and the simultaneous injection of living bacteria which had grown in the water since it was first distilled. He demonstrated that water which stood in laboratories and dispensaries became heavily contaminated.

Hort and Penfold (92) pointed out that intravenous injections of such a variety of substances as plain water, saline, carbohydrates, and proteins, had all been known to cause fever, and that in some of these the fever was probably due to a common cause. They held, as a result of animal experiments, that : (1) There is at present no evidence that salvarsan fever is not necessarily due to organisms grown on water or saline ; and (2) the presence in water or saline of a filter-passing, pyrogenetic substance, which may or may not be a product of bacterial protein, is an important factor in the production of salvarsan, as of other types of injection fever. They found that water which was comparatively free from micro-organisms often produced more fever than that which was grossly contaminated. Also, that water collected at once from the ordinary still of a laboratory or pharmacy often caused marked fever though the water was sterile. They considered it possible that, by aspiration of air on cooling, the water in the receiving tank became contaminated, with the result that a water-soluble pyrogenetic agent was produced which would pass an ordinary filter candle and was not destroyed by autoclaving. They recommended glass boilers and collection of the distillate into sterile vessels, which should be hermetically sealed and autoclaved.

McIntosh, Fildes, and Dearden (93) had come to a different conclusion, and McIntosh (94) subsequently criticized Hort and Penfold's technique. They showed that saline which was kept sterile in Jena flasks from the moment of distillation produced no fever. If contaminated, however, though injected after heat sterilization (the dead bodies of the bacteria remaining in the water), fever resulted. If redistilled, or sterilized by filtration through a Pasteur candle, no reaction resulted. The conclusion was that it was the dead bodies of the bacteria, and not living bacteria, as Wechselmann thought, nor their soluble products, as Hort and Penfold considered, which produced the fever.

Gibbard and Harrison (11) injected fifty-three patients each with 300 c.c. saline prepared from water which had been freshly distilled from an ordinary automatic metal still ; such a still, in fact, as Hort and Penfold would expect to become contaminated with their pyrogenetic agent. One patient had a temperature of 100° F. on the same evening, but the others remained normal. Their conclusions agreed with those of McIntosh and his colleagues, that in fever resulting from saline injections it is the presence of micro-organisms which is important.

The observations have so far taken account only of fever produced by saline itself. Another point of view which must be considered is the effect of

water impurities in raising the toxicity of the arsenical preparation when in contact with it.

Yakimoff and Kohl-Yakimoff (95) showed that the toxicity of ' 606' was increased several times by simultaneous injection of the animal with various micro-organisms, and Ruhemann (96) considered that in some cases reaction may be increased by the presence of micro-organisms in the blood as in septic conditions.

Gonder (97) found that the presence of small quantities of calcium and magnesium (as are found in tap-water), and also that of B. coli and B. pyo-cyaneus in the water, increased the toxicity of ' 606'.

Emery (98), with whom Sicard and Leblanc (99), amongst many others, agree, is very insistent on the importance of excluding impurities from the distilled water. He considers that it is not sufficient to be satisfied merely with the fact that the water is freshly distilled ; when the still is provided with any but a Jena glass condenser it may produce pure water at first, but after a time the steam acts on the glass, which gives off to the water metal and silicates, which add to the toxicity. Some condensers last a very short time, while others may remain satisfactory for two months or so before beginning to produce water which results in the production of reactions. The breaking of an air-cooled condenser made of lead glass led to its replacement and temporary stoppage of a series of reactions (due to silicate of lead) after injections of ' 914 '. The ordinary glass condenser which replaced this gave an immunity from reactions for only eight days, after which silicate of soda appeared in the water and reactions again began to occur. A Bohemian glass, water-cooled apparatus lasted two and a half months, during which time only three slight reactions occurred in 1,200 injections. At the end of this time slight fevers, eruptions, &c., began to occur after injections, and these were mainly abolished by the installation of a new still. Slight symptoms still followed the injections, and it was considered that the practice of autoclaving the water was responsible, since this led to the giving up of impurities by the glass to the water. When the practice of autoclaving the water was abandoned the reactions ceased almost completely. Emery now considers that if a Bohemian glass condenser is used it should be abandoned after distilling about 60 litres, or less if reactions begin to make their appearance. The best still is one made of hard glass throughout.

Dreyfus (100) related a case which was severely upset by a dose of 0·2 grm. when this was dissolved in water from a still which had been in use for two and a half months. When the still was changed the same patient was injected with three times this dose without ill effect.

Schramm (101) holds that it is not sufficient to be satisfied with the absence of metal to chemical tests ; the water should be filtered a number of times through cotton-wool to remove the last traces of metallic impurity.

Lévy-Bing (102) found that severe reactions followed injections of ' 606' whilst he was using a copper still. When the water was treated with sodium carbonate and filtered the reactions ceased. He remarks in support of the catalytic effect of metals that if one dissolved ' 914 ' in water from a copper still

and it was shaken slightly, oxidation occurred very rapidly, the solution turning brown immediately. On the other hand, a solution in water prepared from a hard glass still remained of good colour for some time. He recommended, especially in the case of '914', solution in water which was freshly distilled, stored in Jena glass, treated with carbonate of soda, filtered through a Chamberland candle, and deoxygenated.

Matzenauer (103) drew attention to the possibility of distilled water becoming alkaline and causing reaction.

Ehrlich (104) considered that impurities in the water with which his arsenical preparations are dissolved have an important effect in the causation of reactions, but was unable to say whether this is due to the fact that the tissue cells are unduly sensitized to the arsenic by the impurities, or that the latter act as catalysts in splitting off arsenic from the benzol ring.

Amongst those who do not attach such great importance to impurities in water from the point of view of reactions are Marschalkó and Veszprémi (loc. cit.). These authors found that bacterially contaminated water did not materially increase the toxic effect of '606' for animals, and considered that ordinary bacteria plays only a small part in this respect. It is of interest, however, that in their experiments they had found that 0·1 grm. '606' per kilogram killed five out of ten rabbits when the drug was prepared with presumably pure water. On the other hand, when bacterially contaminated water was used a dose of 0·08 grm. per kilogram killed four out of five animals, so that the contamination appears to have produced an increase in toxicity which was not so trifling as these authors considered. It may be remarked in this connexion that clinically there is a marked difference shown in the respective toxic effects of two samples of '606' which differ by as much as 0·02 grm. per kilogram in their lethal dose for animals. In spite of their sceptical attitude towards its importance, Marschalkó and Veszprémi would always follow the recommendation to use water which was freshly distilled.

Marschalkó considers that the use of 0·9 per cent. saline results in a hypertonic solution which produces more severe reaction, and recommends reduction of the strength of saline to 0·5 per cent. This is now the practice of most workers.

Emery (106) considers that chloride of sodium is a potent factor in the production of reaction and uses distilled water throughout.

Milian (105) holds that, as usually prepared, '606' is insufficiently alkalized, with the result that a mixture of mono- and disodium salts is injected, which is more toxic than a solution containing only the disodium product. He recommends, therefore, that one or two more drops of the 15 per cent. soda solution which is usually used be added after the '606' solution has become clear.

Which of all the above somewhat conflicting opinions is correct ? Which factors are important, and which trivial? A study of the literature is of little assistance towards a decision, because syphilologists have seized upon each new suggestion for the abolition of reaction and incorporated it into their technique. So that when they now claim that the reactions in their practice are infinitesimal, one is at a loss to decide whether it is the use of fresh, double-, or triple-distilled

water, of 0·5 per cent. in place of 0·9 per cent. saline, of hyper-alkalization, of temperature of solutions (as suggested by Schreiber), or the speed at which the remedy is administered, or the preliminary administration of a course of mercury to forestall a Jarisch-Herzheimer reaction. The difficulty is increased when one finds workers who do not break their stills periodically, or who even use tap-water, or add alkali only to the point of clearing the solution, or use 0·9 per cent. saline, and claim equal immunity from side effects. The difficulties are further increased by the varying susceptibility of patients, the numbers to be observed before striking differences in their after-behaviour become apparent, the varying quality of the clinical observations, and lastly, what is probably as important as most factors, the variation in toxicity of different batches of these remedies.

The writer has been engaged for some time investigating, as far as present circumstances will permit, the underlying causes of toxic effect following injections of '606', and certain facts have become clear which may assist towards an explanation.

From clinical observation and animal experiments it is obvious that—

(1) Different batches of '606' vary in their toxicity, particularly in regard to their power of producing vaso-motor symptoms. One may divide batches into two categories from this point of view :

Category A. Safe, even with a technique which is less than good in its attention to detail.

Category B. Safe, if dissolved in water from a good still, alkalized carefully, and strained or filtered before injection, but very liable to cause vaso-motor disturbance if these precautions are not observed.

As an example of this, a certain batch of '606' was noted to be causing more vaso-motor disturbance than usual. The remainder of the batch was sent to Rochester Row, where a hundred and ninety-seven injections of it were given without any untoward effect. Then nine injections were administered after the '606' had been dissolved and prepared with boiled tap-water solutions. Four patients suffered from severe vaso-motor reaction during the injection. It happened that two were susceptible to vaso-motor disturbance, but the other two patients had not previously, nor have they since, suffered from this effect. Experiments on rabbits with this batch showed that—

(i) Prepared with distilled water solutions, 0·12 grm. per kilogram was just tolerated.

(ii) Prepared with tap-water solutions, all rabbits died at once after 0·12 grm. per kilogram, and the maximum tolerable dose of the batch prepared in this manner was 0·10 grm. per kilogram.

Another batch of '606' was treated similarly, and all animals survived doses of 0·13 grm. per kilogram, even though prepared with tap-water. Clinically this batch was very well tolerated.

(2) Other things being equal, tap-water which has not been specially treated (p. 298) increases the toxicity of '606' for animals, and the same applies to alkaline water.

(3) With a batch of Class A above the toxic effect produced by primary solution in tap-water may not be apparent in animals receiving up to 0·12 grm. per kilo, but a cumulative effect is demonstrated by the fact that if a smaller dose is given the following day to the same animals they die, while identically treated controls, using the same batch of ' 606 ' dissolved primarily in saline made from distilled water, survive.

The above appears to indicate that the character of the solution in which the ' 606 ' is dissolved is an important factor in the production of reaction. It is also probable that, even in the absence of noticeable immediate reaction, a technique which pays little attention to the purity of the solution may result in a cumulative toxic effect which is manifested later in the course by signs of intolerance, such as persistent headache, dermatoses, or even death in epileptiform convulsions.

In suggesting the above, the writer fully recognizes the great part which a patient's susceptibility may play, and it is not supposed that all signs of intolerance are the result of faulty technique. The analogy of general anaesthesia might be used in illustration. While the great majority of patients can withstand the onslaught of the most indifferent anaesthetist, with some the care of the most skilful may fail to avert death.

The prophylaxis of side effects has been considered with the discussion as to their aetiology and may be summarized shortly thus :

Patients should be prepared for injection much as for general anaesthesia, and should remain quiet for the remainder of the day, though in the opinion of the writer it is usually possible, especially in the later stages of the course, to allow them to return home after a few hours. The patient should be well housed and clothed, and his diet simple throughout the course.

Solutions should be prepared in water and saline which is above suspicion from the point of view of impurities. In the absence of a still which is above suspicion, the writer believes that solution according to his modification of the method recommended by Taege is equal to that with good distilled water.

In view of the fact that it is impossible to detect an abnormal idiosyncrasy in an otherwise normal patient, the initial dose should be such as can be borne without danger by the most susceptible and the subsequent dosage increased only very gradually. In this respect almost all workers agree that in the absence of any particular contra-indication, 0·3 grm. of ' 606 ' is a safe initial dose for practically every man, 0·2 grm. for women, and 0·05 grm. for infants.

In patients who have previously shown signs of vaso-motor disturbance the prophylactic injection of adrenalin is valuable.

The intervals between injections should have regard to the well-recognized cumulative effect of these arsenical preparations, and it is unsafe to rely entirely on the excretion of arsenic by the urine as a guide to the length of the interval. Generally speaking, however, in the absence of signs of intolerance four-day intervals between doses of 0·3 grm., weekly intervals between doses of 0·4 grm. and 0·5 grm., and a pause of two to three weeks after the administration

of each total of 0·9 grm. are safe. A careful watch should be maintained on the urine for defective diuresis, albuminuria, and casts. Loss of weight, chronic malaise, erythemata, and the signs of intolerance indicated by Milian (p. 324) are valuable indications for reduction of subsequent doses and for increase of intervals beyond the ordinary.

The Treatment of Side Effects.

For vaso-motor disturbance the intramuscular injection of adrenalin as recommended by Milian (p. 316) is generally effective. The dose originally recommended was 1 to 1½ c.c. of a 1 in 1,000 solution, but smaller amounts have often proved effectual.

Ordinary reactions require no further treatment than rest, but for high fever and severe headache most workers recommend aspirin or pyramidon in the usual doses.

In a case of generalized erythema, with high fever and intense headache, the writer once removed 18 oz. of blood by venesection, with immediate relief to the headache, and the fever and erythema had completely disappeared by the following morning. Another similar case, in which severe symptoms were aborted by venesection, was subsequently reported to the writer by Capt. Rawlinson, R.A.M.C. In a third case, intense headache and pruritus were relieved at once by venesection to 10 oz., but the erythema was not aborted. For erythema one would recommend, in addition to phlebotomy, the free use of saline purges and the taking of large quantities of bland liquids.

The treatment of exfoliative dermatitis is troublesome, and there is little guidance from the literature. Calamine lotion and powder, bran baths, and starch poultices are very soothing, while 10 per cent. ichthyol ointment appears to be successful in places where there is much pustulation, but no application has been found to work 'like a charm'. Dieting is important, and meat and eggs seem often to provoke relapses. Paraffin and salines are good aperients, and preferable to mercurial preparations. The patient's body should be carefully protected against chill, especially in cold weather.

For the treatment of epileptiform convulsions most workers recommend phlebotomy followed by saline infusion, and lumbar puncture. Milian and those who have witnessed its good effects in minor cerebral disturbances would in these cases also employ adrenalin.

Neuro-recurrences.

Shortly after '606' came into general use it was noted by numerous observers that symptoms referable to disease of the central nervous system had become much more prevalent, and this constituted the main bases of an attack on the new remedies by Finger (107), Gaucher, and many other syphilologists of high standing.

The symptoms which were chiefly noted were paralysis of one or more cranial nerves, especially the seventh and eighth, but a certain number of cases of paraplegia and hemiplegia were recorded. These untoward sequelae usually came on six to eight or more weeks after the injection. Finger's view, in which he was supported by numerous observers, was that these nerve disturbances were either directly due to the toxic action of ' 606 ', or if syphilitic in nature, they were the consequence of the ' 606 ' having produced a *locus minoris resistentiae* for the parasite. In Finger's cases 9 per cent. had developed cranial nerve trouble after ' 606 ', while in the previous three years he had seen very few similar cases under mercurial treatment. Finger's views were hotly contested by the admirers of the new therapy, some of whom were too zealous and spoilt their case by attempting to prove that such disturbances were no more frequent now than under the old mercurial treatment. There can be no doubt that these cases were much more frequent at that time than they had been under mercurial treatment, although Finger's estimate was considerably higher than the experience of other clinics justified.

Ehrlich's view was that these central nerve disturbances were the result of insufficient treatment. He held that, when the treatment commenced after the disease had become generalized and was insufficient completely to sterilize the patient, certain spirochaetes, situated for example in the membranes surrounding the cranial nerves in their bony canals, eventually woke up and setting up a reaction there destroyed the continuity of the nerve. This view was well supported by the facts collected by Benario (108), which showed briefly that :

(1) In early generalized syphilis the disease affects the meninges almost as frequently as the skin and mucous membranes. The same condition is found in ' neuro-recurrences '.

(2) The incidence of neuro-recurrences is inversely proportional to the amount of treatment which the patients have received.

(3) Prompt treatment with one of the newer arsenical preparations generally results in disappearance of the neuro-recurrence.

This view is well supported by ascertained facts which may be mentioned under the same headings.

1. Ravaut (149) found long ago that in secondary syphilis the cerebro-spinal fluid showed pathological changes in the shape of increased numbers of leucocytes and increase of globulin in 67 per cent. of cases. Altmann and Dreyfus (109) found increase of pressure, cells, or globulin, or a positive Wassermann reaction, or all these combined in nearly 80 per cent. of secondary cases. Gennerich (110) found that nearly 90 per cent. of relapse cases after ' 606 ' treatment showed some pathological change of a syphilitic nature in the cerebro-spinal fluid, and believes that if in the cases of secondary syphilis which show no changes the fluid is examined after a small dose of ' 606 ' or ' 914 ' has been administered (provocative injection) practically every case would be found to have a pathological cerebro-spinal fluid. Ellis and Swift (111) found that 33 per cent. of their secondary

cases showed pathological changes in the fluid, but believe that if the fluid had been examined in all stages the percentage would have been higher.   C. H. Mills (unpublished) in an examination of cases at Rochester Row found increase of cells or of globulin, or a positive Wassermann reaction, or all three in 56·79 per cent. of secondary and 65 per cent. of tertiary cases which showed no symptoms of central nerve-disease.   As an example of the degree of histological change which may be present without manifest clinical symptoms, one patient had 720 cells per c.mm. globulin, and a double plus Wassermann reaction in the equivalent of 0·2 c.c. of fluid.

These facts show the frequency with which the central nervous system is involved in syphilis. Similar changes are found in practically every type of neuro-recurrence or disturbance of the central nervous system after arsenical treatment, and in the few cases which show no changes the symptoms practically always point to syphilitic endarteritis of a cerebral vessel.

2. It is the experience of all that neuro-recurrences have become much less frequent with the gradual increase of arsenical dosage which has occurred as a result of experience.

In this connexion may be quoted the results collected from the French army by Ravaut (48), who reports only two cases of facial paralysis, one of paraplegia, and one of oculo-motor paralysis in the course of 94,762 injections.

A course containing 2·4 grm. '606' (in eight injections) and six mercurial injections, which was instituted by the writer, resulted in five neuro-recurrences in over 10,000 cases.

3. The treatment of neuro-recurrences which is almost unanimously advocated is the prompt administration of '606' or '914' and mercury, and the happiest and most permanent results are obtained when the arsenical preparation is pushed to an extent far beyond what is usual in ordinary routine work.   The writer has not hesitated to administer totals of eight or more grammes of '606' to such cases and has seen nothing but good result from this practice.   This appears to be a complete answer to the contention of those who hold that the newer arsenical preparations have a neurotropic action.   It would be well if those who have to report on neuro-recurrences in the future were to state the exact amount of treatment which the patient had previously received.   Without this information a false impression, which is unjust to the arsenical preparation, may easily be conveyed.

Gennerich's view is that neuro-recurrences are explicable briefly on the following lines. Syphilitic lesions vary in accessibility in this order : skin and mucous membrane lesions, primary sores, meningeal lesions. A treatment which is sufficient only to kill the spirochaetes in the skin and mucous membrane lesions leaves those in the sore to revive and reinfect the body later. The result is reinduration of the sore followed by secondary signs. A treatment which goes farther and sterilizes all but the meninges leaves the spirochaetes to revive there after a time. In this case, owing to the fact that practically the whole army of spirochaetes has been destroyed throughout the body, the tissues of the

latter have developed no immune substance and the reviving spirochaetes find themselves on what is practically virgin soil.   The lesion which results approximates in character and size to that which follows a primary infection, being large and accompanied by considerable sclerosis.   A feeble mercurial treatment results in frequent generalized relapses, the lesions of which balance one another owing to the general development of immune substance.   The burden of the battle is distributed evenly over the body and no vital part suffers at this time.   A more intensive treatment, such as is contained in one or two doses of '606' or '914', suppresses the balancing action of skin and mucous membrane relapses, with their accompanying immunity response, and the meningeal relapse is correspondingly severe.   A still more intensive, yet insufficient, treatment would suppress the spirochaetes in skin and mucous membrane and in the primary sore, and damage those in the meninges so severely that they would revive only slowly.   The result in this case would be that the only evidence of the relapse at first would be changes in the cerebro-spinal fluid.

Whatever the theory may be as to their exact aetiology, there can be no question that the prophylaxis of neuro-recurrences lies in a sufficient arsenical and mercurial treatment when the patient first appears.   It is a strange fact, however, that although this fact has been established for some years now, there can still be found practitioners who will administer one or perhaps two doses of an arsenical preparation and allow the patient to go away unfurnished with any advice as to continuance of treatment, as two patients at present at Rochester Row know to their cost.   One of these is slowly recovering from a hemiplegia which bids fair to leave him with a permanent monoplegia of the right arm; the other is recovering from a complete paraplegia.   Both were treated in the first place as just described.

The Contra-indications of '606' and '914'.

These may be divided into absolute and relative.

The absolute contra-indications have become considerably reduced with experience as to the safety of small doses, controlled by careful observation of their side effects, and at present one would exclude only cases of Addison's disease, bleeders, and those suffering from such advanced visceral disease that death must inevitably follow in a short time.

Relative contra-indications. There is a fairly general agreement as to the diseases the presence of which is an indication for caution as to dosage, &c. These are visceral lesions such as myocarditis, renal and hepatic disease, arteriosclerosis, aneurism, diabetes, and advanced disease of the central nervous system. Pregnancy, though hardly a disease, also requires caution.

Visceral diseases may be syphilitic or otherwise.   In those which are syphilitic there is the fear that the exhibition of a large single dose at first may cause such a severe Jarisch-Herxheimer reaction that the organ is fatally damaged.   In this connexion may be mentioned syphilitic disease of the central

nervous system, where it is possible that a process affecting vital centres, either directly or through their arterial supply, may temporarily become so aggravated as to lead to the death of the affected centre. The cases recorded by Ehrlich above (p. 326), in which cranial nerves became temporarily paralysed, are examples of the same effect, though with less disastrous consequences, while a certain number of cases have been recorded in which paraplegia or hemiplegia have followed the first full dose. Similarly in cases of syphilitic myocarditis and in aneurism or aortic regurgitation, or in cases which suffer from angina pectoris, in all of which there is reason to believe that the coronary arteries are diseased, it is clear that a Jarisch-Herxheimer reaction would be extremely dangerous. The same applies to severe syphilitic disease of the larynx.

In connexion with disease due to other causes than syphilis, it will be recalled that the observations recorded above seemed to indicate that the remedies under discussion primarily damage capillaries, especially if these are in an abnormal state on account of existing disease. The existence of renal disease is important in this connexion. Although it is recognized that the arsenical preparation can be given to patients suffering from mild albuminuria, even with casts, the indications are naturally for caution, since not only may a toxic dose precipitate, a severe nephritis, but severe symptoms may result from undue retention of the remedy in the body. The occasions, however, on which any anxiety is provoked by the presence of renal disease are extremely rare. It is usually found that patients suffering from albuminuria in the early stages of syphilis clear up in this respect after the first small dose, the albuminuria having clearly been syphilitic in nature.

The tendency to haemorrhages after injections emphasizes the need for caution in cases of gumma of the brain, an example of which is a case recorded by Duguid and Graham (112) in which a patient died seven days after a dose of 0·6 grm. ' 606 ', and post mortem was found a gumma, four centimetres in diameter, external to the anterior horn of the right lateral ventricle, which was surrounded by a considerable effusion of blood.

Alcoholics have already been mentioned as being susceptible to the toxic effects of ' 606 ' and ' 914 ', and naturally come under the category of cases in which the arsenical preparations are relatively contra-indicated.

Attention does not appear to have been drawn to the care which should be exercised where the patient is constitutionally liable to dermatoses, such as eczema, erythema, and urticaria. In these it is reasonable to suppose that the skin vessels are in an abnormal state and likely to be still further damaged by the arsenical preparation, unless this is administered with due regard to its cumulative effect.

Caution with regard to patients under the above categories applies not only to individual doses but to intervals between injections, or, in other words, to the total amount of the remedy administered within a given period. It is impossible to state in detail how each of the above cases should be managed, but by commencing with a dose of 0·1 or 0·15 grm. ' 606 ', increasing the intervals by

20–100 per cent., and watching carefully for the signs of intolerance mentioned above, a safe course can usually be steered. The writer has found that an intra-muscular injection of 0·2 grm. '914' is a useful procedure in commencing the treatment of cases where there is reason to fear the result of severe reaction.

Dosage in Cases where there is no particular Contra-indication.

This has already been referred to in connexion with the prevention of side effects, but the practice of different workers may be mentioned here in more detail.

Few or none would now employ a dosage such as that used by Schreiber (17) at first with '914', namely 0·9, 1·2, 1·35, and 1·5 grm. at intervals of two days, although his paper was written with an experience of 230 cases treated without ill effect. A number of deaths occurred in other clinics as the result of the employment of this dosage, and Schreiber (113) subsequently modified it very considerably.

Neisser (114) would commence with a dose of 0·1 to 0·2 grm., rising gradually and leaving intervals of ten days between doses when these have reached 0·4 to 0·6 grm. Kromayer (115) was probably the first to recommend frequent small doses, giving 0·1 to 0·2 grm. three times a week to a total of 3·6 grm. Leredde (116), who is a believer in pushing the remedy in the later stages, insists on a small initial dose (0·1 grm. '914' followed by 0·3 grm. in eight days). Gennerich (83) commences his cases generally with a dose of 0·15 grm. '606', while Emery, as also Fordyce (117), usually commences with 0·3 grm. for men who are quite well.

These examples will serve to show the general recognition of the necessity for caution which now prevails with regard to initial dosage. Similarly, recognizing the cumulative effect of these remedies, the former practice of administering large doses at short intervals has ceased, and the general custom now is to allow an interval of 7–10 days after the dose has reached 0·4 grm. '606', or its equivalent in '914'.

Although the consensus of opinion is in favour of a cautious commencement in all cases, it is equally unanimous as to the necessity for administering a sufficiently large quantity to ensure immunity from recurrence, and in con-demnation of the practice, which still unfortunately prevails in some quarters, of giving only one or two doses. Details regarding the full courses described by representative workers will be given later when the general management of syphilis is considered.

The Respective Merits of '606' and '914'.

Opinions are divided as to whether '914' is equal therapeutically to '606'. Most will agree that in immediate effect it is difficult to choose between them, but it is also difficult to overlook the opinion of such authorities as Gennerich

and Dreyfus, amongst others, who hold as the result of later observation that '914' is not so powerful or permanent in its therapeutic effect.

Probably this has to do with the more rapid excretion of '914' after intravenous injections, as has been shown above, since Wechselmann and Eicke have stated their opinion, with which the writer concurs, that when administered subcutaneously, so that it is excreted more slowly, '914' gives better results than follow the intravenous injection of '606'.

As to toxicity, it seems probable that, as pointed out by Schreiber in the first place, under a good technique '914' has the advantage. It must be remembered, however, that '914' is a much more labile preparation and that errors in technique, such as impurities in the solvent when it is given dilute and delay in administering it, are visited with more certainty by serious afterconsequences.

Galyl.

Mouneyrat (118) introduced in 1913 two new preparations, tetraoxy-diphosph-amino-diarsenobenzene or 'galyl' and phenyl-disulph-amino-tetraoxy-diamino-diarsenobenzene or 'ludyl', of which the former has survived and come into extensive use during the war. It is a greenish grey powder which is sold in ampoules, like the preparations already mentioned, and is prepared for administration by simple solution in distilled water, which produces an alkaline solution. This may be injected either dilute or concentrated, and the doses usually recommended are 0·3 to 0·4 grm. intravenously. The indications and contra-indications of galyl are similar to those of the other preparations.

The immediate effect of galyl on syphilitic lesions and on the Spirochaeta pallida is similar to that of '606' or '914', but no accurate statistics are available as to the permanence of the results, since most of the reports make no reference to subsequent observation. As the result of later observation of patients who were treated with this remedy earlier in the war, the writer is of opinion that galyl is not so powerful as the older preparations.

It has been claimed for it that galyl is less toxic, its intravenous injection not being followed by the vaso-motor disturbances which sometimes occur after injections of the other preparations. This claim cannot be substantiated in view of the record as to reactions reported by Ravaut (48), which includes one case of epileptiform convulsions, three of albuminuria, two of jaundice, four of erythema, pruritus, and urticaria, and frequent vaso-motor disturbances in the course of 8,846 injections. This compares with seven cases of albuminuria, one of transient coma, one of epileptiform convulsions, two of meningism, sixteen of jaundice, twenty-three of vertigo, twenty-five of vaso-motor disturbance, twenty-two dermatoses, and ten cases of oedema of the face which resulted from 82,333 injections of '606' and '914'. The opinion of Ravaut is that galyl is inconstant in make and solubility and more liable to be followed by untoward side effects.

For this reason the medical officers on whose report he writes have rarely exceeded 0·2 grm.   At Rochester Row one case of severe exfoliative dermatitis has followed injections of this remedy.

Galyl is also prepared for administration intramuscularly, being suspended in a fatty basis.   Injected in this form it does not cause a great amount of pain, but in the hands of Harrison, White, and Mills (loc. cit.), doses of 0·4 grm. failed to cause spirochaetes to disappear, and the opinion of these writers was that its effect is not equal to that of ' 914 ' administered by the same method.

Luargol.

Luargol is a combination of dioxy-diamino-arsenobenzine with antimony and silver.

The desirability of bringing more than one remedy to bear at one time on the treatment of protozoal diseases was recognized by Ehrlich (86) as the result of his experiments on the chemotherapy of trypanosomiasis.   Considering that their great parasitotropic properties are due to the affinity for the parasite of the groups to which the arsenic is bound, he compared his arsenical remedies to a poisoned arrow of which the shaft is the benzol, the point the amido group, and the poison the trivalent arsenic.   Continuing the analogy, he said, ' Now, it is a frequent practice of many uncivilized peoples, in order to be certain of killing their enemies, that they not only rub over their arrows with one kind of poison but with two or three totally different kinds, and so it has also appeared advisable to imitate this procedure against the parasites and to poison our synthetic arrows not singly but doubly.'

On this principle, with Karrer, he produced salvarsan-copper, a preparation which has been used with success in yaws and leprosy.   On the same hypothesis, Danysz has combined dioxy-diamido-arsenobenzol with silver bromide and antimony.   Silver bromide was shown by Danysz (119) to be a better antiseptic than the chloride or nitrate, and antimony has long been a proved spirochaeticidal agent.   Thus Ranken (120) showed that finely divided antimony (Plimmer) had an excellent effect in yaws.   Tsuzuki (121) claimed good results in syphilis from antiluetin, or bitartrate potass-ammonium antimonium oxide, while Uhlenhuth, Mulzer, and Huegel (122) found that benzol-sulphon-para-amino-phenyl-stibinate of soda and para-urethane-phenyl-stibinate of soda had a good effect on hen spirochaetes.

The combination of Danysz, now known as luargol or ' 102 ', was shown to be seventy-five times more active than atoxyl and ten times more active than ' 606 ' against typanosomes.   Renault, Fournier, and Guénot (123) treated 500 primary and secondary syphilitic cases with luargol, using doses of 0·10 grm., which were increased gradually at intervals of three or four days to 0·3 or 0·35 grm., making a total of 1·2 to 1·5 grm. in six or seven injections.   There was little reaction, but two cases developed a transient erythema.   Spirochaetes

disappeared from lesions as rapidly after injections of 0·10 to 0·15 grm. luargol as after 0·3 to 0·4 grm. ' 606 ', and the clinical results were equally good. Primary cases with a negative Wassermann reaction remained negative. Secondary cases varied in this respect, but the results with them which were obtained by injections of luargol were not inferior to those produced by two or three times as much ' 606 '.

Other workers have reported similar results. Dalimier and Lévy-Franckel (124) treated a number of cases of very severe and malignant syphilis and obtained results with comparatively small doses of luargol which were, if anything, more rapid than those produced by much larger doses of ' 606 ' or ' 914 '.

Bonard (125) reported equally favourably in a paper which detailed the chemical and biological foundation of luargol. At Rochester Row the immediate results have confirmed what has already been written. The reaction following injection of luargol is usually trivial, though one case of transient erythema was observed. Spirochaetes disappear rapidly after doses as small as 0·10 grm. and the clinical effect is equally prompt. The effect on the Wassermann reaction has not been worked out on a sufficiently large number of cases to justify any conclusion, but the results up to the present have compared favourably with those obtained by ' 606 ' intravenously.

A disadvantage of luargol as first introduced was the thrombosis of veins which it caused at the site of injection. This was possibly due to the great alkalinity of the solution, though the same effect was produced when this was very dilute. This disadvantage has now been overcome by the introduction of disodoluargol, a dark-brown powder, rather like emery powder, which is ready for use when dissolved in distilled water, which produces a very dark-brown solution. It can be given dilute, or concentrated like ' 914 ' or galyl, and has the further advantage that it is much more stable than ' 914 '. A number of doses kindly furnished to the writer were weighed out from a stoppered bottle, without any particular precaution as to exclusion of air, and injected after a week or more without ill effect. The indications and contra-indications of luargol are similar to those of the other preparations. As to dosage and the management of syphilis generally with this preparation, it is too early to speak. At Rochester Row doses of 0·3 grm. are given weekly for seven weeks as a minimum, in combination with mercury. If it fulfils its present promise, disodoluargol will have many advantages, but as to that point it is for the future to decide.

Mercurial Preparations.

The discovery of ' 606 ' and allied preparations has stimulated considerable research directed to the discovery on the same lines of a compound of mercury which would be less toxic and of greater efficacy than those in routine use at the present moment. But although a number of compounds have been synthesized

which promised well in animal experiments it cannot be said that the position of the older preparations has yet been disturbed.

Blumenthal (126), and Blumenthal and Oppenheim (127), have advocated the use of acetyl-aminol-mercury-benzoate of soda or 'toxynon', an aromatic compound in which the mercury is attached directly to the benzol ring. It contains 48 per cent. of mercury and is stated to be well tolerated. Gutmann (128), reporting on this preparation, found its toxicity to be about two-thirds that of the salicylate. For administration to men he used a one in fifteen solution and gave a dose of 0·1 grm. intravenously, which was repeated on the following day. On the fourth day the dose was increased to 0·15 or 0·2 grm., and injections were repeated at suitable intervals until eventually 3 grm. had been administered in six weeks. In spite of the advantage of its comparatively low toxicity toxynon has not, however, proved to have practical advantages over other preparations.

Kolle and Rothermundt, in association with Dale (129) and with Peschic (130), conducted a very exhaustive research into the toxicity and spirochaeticidal properties of various mercurial salts and organic compounds against hen spirochaetes, and found that experimentally the most suitable preparation was disulph-amino-dimethyl-phenyl-pyrazolon mercury (Scheitlin), an insoluble compound containing 40 per cent. mercury and now known as 'argulan'. They found in hen spirochaetosis that the relation between the curative and the minimum lethal dose of this compound $\frac{DC}{DT}$ was $\frac{1}{100}$, the nearest approach to this being calomel with a $\frac{DC}{DT}$ of $\frac{1}{60}$. Mintberger gave argulan in an oily suspension in doses of 0·3 grm. every three to six days, but found it painful and slow in its effects on syphilitic lesions.

Queyrat (131) advocated amalgams of mercury and silver and of mercury and platinum, reporting good results from each when other preparations had partially failed.

Schreiber (132) has investigated combinations of mercury with various aniline dyes on the principle that the latter may reduce the toxicity. After considerable research on animals he has tested certain of these preparations on man, viz. combinations of mercury with tetra-iodo-phenolphthalein ('nosophen'), with erythrosin, and with methyl-erythrosin, but without obtaining any striking results. Erythrosin mercury was certainly effective, but rather toxic and provocative of considerable local reaction.

Abelin (133) concluded a long investigation into the chemical and toxicological properties of mercurial compounds with the remarks that (1) toxicity and therapeutic efficacy do not run *passi passu* (as is commonly supposed), and (2) that the most easily ionized and most toxic salts—the perchloride, succinimide, and calomel—are therapeutically less preferable than the less easily ionized and less toxic aromatic compounds, such as the salicylate.

Schamberg, Kolmer, and Raiziss (134), after a very exhaustive research,

agree with the belief expressed above that it is the chemical combination in which mercury is presented to the tissues and to the parasites which affects its relative action on each—in other words, its $\dfrac{DC}{DT}$. After pointing out that remedies which destroy trypanosomes similarly affect the spirochaetes of syphilis, they announce a group of new organic mercurial compounds which have been prepared by them and some of which, though less toxic than perchloride of mercury, have a stronger destructive action on trypanosomes. Incidentally, one of these—'No. 99'—was also shown to have a fifty times greater bactericidal power against staphylococci than perchloride *in vitro*, while in the presence of serum its bactericidal power was two hundred times greater. It is too painful for intramuscular injection and is being tried intravenously.

Colloidal preparations of mercury had not proved a great success up to date, possibly because they were too weak in mercurial contents. Recently, however, a colloid preparation has been produced by Crookes Laboratories in 1 per cent. and 5 per cent. strengths. It is stated by McDonagh (150) to be as powerful in a full dose (15 c.c.) of the 1 per cent. strength when administered intravenously as three full doses of salvarsan. This statement was not borne out by the experience at Rochester Row, where, on clinical as well as microscopical evidence, the immediate effect of 10 c.c. collosol mercury was found to be not nearly so powerful as that of 0·3 grm. '606'. Clinical lesions did not clear up nor did spirochaetes disappear from them any more rapidly after intravenous injections of collosol mercury than after ordinary intramuscular injections of mercurial cream, let alone salvarsan. Collosol mercury may eventually prove to be a valuable preparation for use in the treatment of syphilis, but it is hardly out of the laboratory stage yet and it is not altogether non-toxic. In large doses it produces the usual symptoms of mercurial poisoning, and since 2·5 c.c. of 1 per cent. collosol mercury is the lethal dose for an ordinary sized rabbit, one would judge, from a somewhat extensive experience of the transfer of mercurial experiments on rabbits to man, that 15 c.c. is close to the border-line of tolerance even for a single dose. A rabbit of 1 kilogram will just survive 25 mg. succinimide of mercury injected intramuscularly, while a man may be upset by 100 mg. These figures correspond pretty closely with those for collosol mercury, and when it is remembered that the dose must be repeated it will be seen that the introduction of collosol mercury into general use at present may not be devoid of danger.

The enormous amount of work disclosed by the above survey has not, as mentioned above, yet resulted in a compound to displace the older, well-known preparations—metallic mercury, calomel, and salicylate of mercury amongst the insoluble, and the perchloride, succinimide, bibromide, biniodide, and benzoate of mercury amongst the soluble.

As to administration, the choice for routine use rests between injection, inunction, and the oral method. The last-named is not generally favoured in the early stages of syphilis on account of the uncertainty of absorption and the

liability to gastric and intestinal disturbance which it entails.   In certain cases, however, oral administration may be valuable.   Thus, after the patient has received a considerable amount of treatment with injections of ' 606 ' and mercury it may be impracticable for him to continue under such close supervision as these entail.   In such cases the writer is in the habit of prescribing a pill or tabloid of grey powder or of grey powder and Dover's powder in order to maintain the effect.   A brochure published in France by the Sous-Secrétariat d'État du Service de Santé (135) recommends that after the early intensive course of mercurial and arsenical injections the patient should take for the first ten days of every month a pill containing 0·05 grm. protoiodide of mercury and 0·01 grm. extract of opium, commencing one month after leaving hospital and continuing for one year.

Between injections and inunctions opinions are evenly divided.   There is no doubt that as good, if not better, results are obtained by well-administered inunctions as by injections, but nobody will deny that inunctions to be effective require skill and conscientious application, as a study of the monograph by Reginald Hayes (136) on the subject will show.   Injections have the advantage of convenience and certainty.   Their technique is fairly easily learnt, and the matter is entirely in the hands of the medical attendant himself.   The dose is definitely placed in the tissues, and the administration of the remedy does not depend either on the patient's memory or on the energy of his attendant.

Injections may be intravenous or intramuscular.   The former have not enjoyed a great popularity for routine use, but in cases where a quick effect is desired without resort to arsenical preparations the intravenous injection of the cyanide (1 c.c. of a 1 per cent. solution) or of the perchloride, daily or on alternate days, has proved valuable.   Administered in this manner, however, mercury may rapidly produce toxic symptoms—dysenteric diarrhoea, nephritis, and severe stomatitis.

Regarding the preparations for intramuscular injection, a close discussion as to the respective merits of the soluble and the insoluble preparations would be useless.   Each has its equally powerful advocates, and the choice of each very largely depends on circumstances.   Probably the great advantage of the soluble preparations is that owing to the speed at which they are absorbed their effect is more rapid, and also it is possible to approach with them more nearly to the toxic dose.   On the other hand, the rapid absorption of the soluble preparations in an active form makes it impossible to inject at one time sufficient mercury to last for some days, so that injections must be given daily or on alternate days. Biniodide of mercury, 1 c.c. of a 1 per cent. solution, is recommended for use in the French army, where the bibromide and the benzoate are also employed.   Fordyce (117) prefers the perchloride, gr. $\frac{1}{10}-\frac{1}{5}$ every day or every other day.

The insoluble preparations have the great advantage that a single dose will usually suffice for a week's treatment, though probably the effect is not so rapid as that of the soluble preparations.   Another advantage is that the effect is kept

up for a much longer time after the course of injections has ceased, since the mercury continues to be absorbed from the site of the injection for some weeks. From another point of view this is a slight disadvantage, since a patient cannot be watched so closely for signs of intolerance. Thus, an overdose of a soluble preparation would rapidly produce symptoms and give warning not to repeat the dose, while in the case of an insoluble preparation the symptoms are apt to continue long after suspending treatment.

The insoluble preparations in most common use are metallic mercury in a state of fine subdivision, calomel, and mercury salicylate. Calomel and metallic mercury are suspended in an oily basis of which there are numerous formulae, the most popular in the army being that associated with the name of the late Col. Lambkin. It contains creosote and camphor (20 per cent.) in a palmitin base, and the most usual strength is 10 per cent. The formula used largely in the navy is similar but contains chlorbutol, and its strength is 20 per cent. The salicylate is most conveniently suspended in liquid paraffin. The usual weekly dose of calomel varies from $\frac{1}{2}$ to 1 gr., that of mercury from $\frac{1}{2}$ to $1\frac{1}{2}$ gr., and that of the salicylate from 1 to 2 gr.

As to the choice between these preparations, it is difficult. Gennerich and others prefer calomel for its quicker and more intensive effect, but after trying this preparation for some time the writer came to the conclusion that for the combined arsenical and mercurial treatment metallic mercury has many advantages. It is more easily tolerated both locally and generally, and although its effect is not so rapid as that of calomel it is more lasting. After all, if one employs the newer arsenical preparations one does not look to the mercury for rapidity of effect. The rôle of mercury in the combined treatment would appear rather to be that of an agent by which the effect of the arsenical preparation is maintained for long after the latter has been excreted.

Iodine.

The position of potassium and sodium iodides has not been materially disturbed by more elaborate preparations. Although, as McIntosh and Fildes have shown, their antispirochaetal power is nil, they are acknowledged by practically all as invaluable adjuvants to the more specific treatment.

Recently a colloidal preparation of iodine—collosol iodine—has been used by various workers, though little has been published regarding it. McDonagh considers it is more powerful than any other preparation of iodine and is practically never followed by iodism. On the suggestion of Sir Malcolm Morris, the writer investigated collosol iodine from the point of view of its power of intensifying the action of '606'. In sixteen cases suffering from syphilitic lesions in which spirochaetes were easily demonstrable, an intravenous injection of 100 c.c. collosol iodine, followed in twenty-four hours by an intravenous injection of 0·1 grm. '606', resulted in disappearance of spirochaetes from the lesions of eight. Controls treated with 0·1 grm. '606' without preceding iodine

showed spirochaetes twenty-four hours later in every case.   In twenty-five cases, each of the seven doses of a course of '606' was preceded twenty-four hours previously with an intravenous injection of 100 c.c. collosol iodine, with the object of determining whether such a course would result in a higher proportion of negative Wassermann reactions than under routine treatment. Seven cases which were negative at first were negative at the end of the course ; of the remaining eighteen, ten were negative, five positive, and three weakly positive.   As far as these results went, therefore, they showed no particular advantage in respect of the Wassermann reaction over treatment without iodine.   Unfortunately the preparation of collosol iodine was found to be causing an undue amount of thrombosis in the injected veins, and a further opportunity of testing a new preparation of collosol iodine has not since occurred.

Iron and Sulphur Compounds.

Two preparations have recently been introduced by McDonagh for the treatment of syphilis, and it was claimed by him that they are superior in many respects to the arsenical remedies which have already been discussed.   For the chemical and biological principles on which this author bases his views reference must be made to his work on the subject (137), as lack of space prevents its discussion here.

One of the preparations, ferrivine, is tripara-amino-ferric-benzene-sulphonate and the other is intramine or diortho-amino-thio-benzene, the two remedies being used in conjunction.   As first introduced, ferrivine was injected intravenously.   It usually gave rise to alarming symptoms of dyspnoea and shock on the table, and was described by Sequeira (138) as the most efficient emetic he knew.   Intramine was injected intramuscularly, but a form in which it can be administered intravenously has more recently been introduced, probably on account of the intense pain to which the intramuscular injections gave rise. The merits of these remedies have been fairly extensively discussed and various views expressed.   At a meeting of the Royal Society of Medicine (138) Shillitoe and Pringle expressed themselves favourably.   Harrison pointed out that both of these remedies, given precisely according to the directions of their author, were extremely unpleasant in their side effects, and had absolutely failed to affect spirochaetes in three cases of syphilis or to influence them clinically, while in one case fresh lesions had made their appearance during the treatment.   Mills pointed out that one of the cases produced by McDonagh to illustrate the good effect of his remedies was still showing an anal mucous patch and a syphilitic throat after two months' treatment.   Subsequently a somewhat polemical discussion followed in the medical press (139), in which McDonagh stated that the influence of a remedy on the Spirochaeta pallida or the reappearance of syphilitic lesions during treatment were not criteria by which an antisyphilitic remedy could be judged.   Ferrivine, however, has apparently been withdrawn, its author

not having yet been able to rid it of the disadvantages complained of by Sequeira, Harrison, and Mills.

THE GENERAL MANAGEMENT OF SYPHILIS.

It will be convenient to discuss the general treatment of syphilis from the points of view of (1) syphilis in which there is no clinical evidence of disease of the central nervous system, and (2) syphilitic disease of the central nervous system.

The treatment of syphilis without obvious signs of disease of the central nervous system. All workers are unanimous on the importance of commencing treatment as long as possible before the Wassermann reaction becomes positive. All results show that cases treated in the early primary stage suffer far less from relapse, whether clinical or serological, than those in which treatment was delayed until later. The necessity of energetic local treatment of the primary sore is also generally insisted upon, experience having shown that relapses after arsenical treatment very often manifest themselves first as re-induration of the primary lesion. The general explanation of this fact is that in a well-developed primary sore many of the spirochaetes are inaccessible to remedies circulating in the blood and so escape destruction. Excision, cauterization, and the application of 30 per cent. calomel ointment are the favourite methods of local treatment of the primary sore which have been adopted. In a sore which cannot be removed bodily or cauterized, the writer's usual plan is to provide the patient with a pre-scription for the Metchnikoff ointment, viz.: Calomel 33 parts, lanoline 67, and vaseline 10, and to advise the patient to 'try to rub the sore away with it'. At Rochester Row, Mr. C. H. Mills has had considerable success in reducing the induration of primary sores by injecting them with hectine in a dose of 0·2 grm. as supplied in ampoules ready for use.

As to the amount of treatment required for any given case, all are agreed that it is impossible to lay down any definite rule, since no course has yet been devised which will ensure 100 per cent. of cures. Experience has shown that it is impossible to state definitely on commencing treatment how many grammes of '606' and of mercury will be necessary to ensure a cure, and the almost universal practice is to lay down a minimum course and to determine the addi-tional which may be required by the behaviour of the Wassermann reaction of the blood, supplemented often by periodical examinations of the cerebro-spinal fluid. The necessity for subsequent observation of the patient after cessation of treatment is generally insisted upon, and here again it is becoming much more common not to be contented with a simple examination of the blood serum and cerebro-spinal fluid at intervals, but to institute after a given period a provoca-tive injection of one of the arsenical preparations with the object of stirring into fresh activity any spirochaetes which may be lying latent. The provocative injection (of, say, 0·3 grm. '606') is followed by Wassermann tests of the blood

serum after two, four, eight, thirteen, and twenty-one days, the tests being carried out at these spaced intervals in order that a fleeting reaction on the one hand, or a delayed one on the other, may not be missed. The fluid may be tested one week after the injection. The following are minimum courses adopted by different representative workers :

Neisser (114) prescribes a course of 2·5 to 3 grm. of ' 606 ', injections being given on the first, tenth, thirtieth, fortieth, and fifty-fifth days. The treatment is combined with mercury, and a second, similar course administered after an interval.

Leredde (116) relies entirely on the arsenical preparation, seeing no logical reason for the combination with mercury. The treatment is continued until the blood reaction is negative to both the original Wassermann test and Hecht's modification, when an examination is made of the cerebro-spinal fluid. If the latter shows the slightest change the treatment is resumed after a suitable interval. One of the two following methods is usually adopted :

Day of Treatment.	Doses of ' 914 '.	
	1st Method.	2nd Method.
	grm.	grm.
1	0·15	0·15
8	0·2	0·2
15	0·3	0·3
22	0·6	0·6
29	0·9	0·9
36	—	1·2
43	—	1·2
50	—	1·35
51	0·6	—
58	0·9	—
65	1·2	—
71	—	0·45
78	—	0·6
86	0·6	0·9
93	0·9	1·05
100	1·2	—

It will be seen that the second method is more intensive than the first, and the author remarks that it may have to be interrupted on account of symptoms of intolerance. One month after completing the course a provocative injection is given, followed by four Wassermann tests between the succeeding fifth and thirtieth days.

Emery (140) gives a course of six injections at the rate of two weekly in doses of 0·3 to 0·4 grm. for men, and repeats the course after an interval of fifteen days. He combines the treatment with mercurial injections.

Fordyce (117) gives, in one course, five to six injections of 0·3 to 0·4 grm. ' 606 ' for men and 0·25 to 0·3 grm. for women, at intervals of eight to ten days. This is combined with twenty to thirty injections of perchloride of mercury, gr. $\frac{1}{10}$ to $\frac{1}{5}$, at intervals of one to two days, or ten to thirteen injections of mercurial cream or salicylate of mercury. He prefers the soluble preparation of mercury whenever he can get the patient to attend sufficiently frequently. Primary cases with a negative Wassermann reaction are treated with two such

courses. In secondary cases the arsenical treatment is preceded by several injections of a soluble preparation of mercury. Patients in the tertiary stage are treated according to circumstances, and the main trust here is placed in mercury and iodides.

Gennerich (13) gives to primary cases with a negative Wassermann reaction six to eight intravenous injections of 0·3 to 0·5 grm. '606' and fifteen intramuscular injections of calomel (0·03 to 0·05 grm.). In primary cases with a positive Wassermann reaction the above course is followed up by a second one consisting of three to four injections of '606' after an interval of three weeks. Secondary cases are treated with six to eight injections of calomel before the '606' is commenced, and the calomel is continued in combination with the '606' until fifteen injections have been given. Commencing with small doses of '606', these are gradually increased to 0·4 or 0·5 grm., allowing short intervals between the small doses and not less than one week between those of 0·5 grm., until ten to twelve injections have been given. If the Wassermann reaction does not quickly become negative in the first course, the latter is succeeded after an interval of thirty days by a follow-up course of four injections of '606'. A third course may be given after a similar interval, according to the behaviour of the blood and cerebro-spinal fluid. The mercurial treatment is regulated with reference to the number of preceding injections. After the fifteenth injection of calomel has been given an interval of eight weeks is allowed to elapse before a second similar course of calomel is administered. Women receive correspondingly less doses, and those who weigh less than 40 to 50 kilograms, or who are pregnant, receive no mercury. Pregnant women are treated with three courses similar to the above, with intervals of thirty days between courses. For the first course '606' is used, and for the second and third, on account of its milder effect, '914' is preferred. Otherwise, for ordinary cases Gennerich is not a believer in '914'. Patients in later stages of syphilis are treated with a number of courses, each consisting of six intravenous injections of '606' and ten to fifteen of calomel, with intervals of seven to nine weeks between courses.

The treatment is controlled throughout by examination of the cerebro-spinal fluid and of the blood. After a year from cessation of treatment in early cases a provocative injection of '606' is given, and this is followed by a Wassermann test of the blood and cerebro-spinal fluid. Gennerich insists that it is possible to abort syphilis only when treatment commences in the primary and early secondary stages, and that in later stages the treatment should be carried out on the chronic intermittent plan. His results in early stages of syphilis have already been detailed (p. 294).

Wechselmann (39), as already mentioned, trusts entirely to the arsenical preparation, and the following is a specimen of the treatment adopted for a case of secondary syphilis:

Day of Treatment.	'914' subcutaneously.	'606' intravenously.
	grm.	grm.
1	0·45	
4	—	0·3
7	0·3	—
11	—	0·3
15	0·45	—
18	—	0·4
23	0·45	—
26	—	0·3
30	0·45	—
37	—	0·3
41	0·45	—
44	—	0·2
48	0·3	—
51	0·3	—
59	0·3	—
62	0·3	—
64	—	0·3
67	0·45	—
70	—	0·35
76	—	0·3

The length of the above course is explained by the fact that the Wassermann reaction was not completely negative until two months after commencement. The cerebro-spinal fluid was examined once and fourteen Wassermann tests were carried out on the blood.

The course recommended for use in the French army is designed for two purposes: (1) to render the soldier fit to return to his unit as quickly as possible, and (2) to complete his cure after his return to duty. In the first place, eight intravenous injections of '914' are administered in increasing doses at intervals of six days, the patient being in hospital. In addition to this, forty-two injections of a soluble salt of mercury, or fifty inunctions, are administered. At the end of this course, which lasts seven weeks, the patient returns to his corps and one month later commences to take pills of protoiodide of mercury (0·05 grm.) with extract of opium, one of which is taken for the first ten days of every month for a year.

The minimum course prescribed at Rochester Row to average early cases of syphilis in the British army at the present moment is as shown below.

Day of Treatment.	Doses of '606' injected intravenously.	Mercurial Cream injected intramuscularly.
	grm.	gr.
1	0·3	1
4	0·3	—
8	0·3	1
15	—	1
22	0·4	1
29	0·5	1
36	—	1
43	0·5	1
50	0·5	1
52	Wassermann test. If this is not completely negative, potassium iodide for two weeks, followed by	
69	0·3	1
76	0·4	1
83	0·5	1

If the blood is still positive, a series of short courses is prescribed, similar

to that from the sixty-ninth to the eighty-third day, with about a month's interval between the courses, and commencing again about the hundredth day; or chronic mercurial treatment, according to circumstances.

If the blood is found to be negative on the fifty-second day treatment is suspended, and the patient observed at monthly intervals, if this is practicable. (At the present moment it is generally impracticable to observe patients beyond the date of the negative Wassermann, since they are drafted away for military service.) It would probably be better to give the whole course from the first to the eighty-third day, whatever the result of the Wassermann on the fifty-second day, and this is done in certain special cases.

The above course is modified under the following circumstances : In tertiary, late secondary, and all old recurrent cases where the previous treatment has been scanty, and the Wassermann reaction is strongly positive at the time the patient appears for treatment, no particular attention is paid to the Wassermann reaction on the fifty-second day. There is little hope of obtaining a lasting negative at this stage, and, provided that all lesions have healed by the fiftieth day (which is practically always the case), the further treatment generally advised is that mentioned above for cases which remain positive after the eighty-third day of treatment. These cases differ very greatly, and no hard-and-fast rule can be laid down for them. The main principle for guidance in their management is that treatment must be prolonged over a number of years, as an insurance against worse manifestations of the disease.

In place of intravenous injections a number of patients are now being treated by the intramuscular method, the dose at each injection being 0·6 grm. of ' 914 ', and the interval one week. The soldier usually remains in hospital only so long as is necessary to allow open lesions to heal up, and he then attends as an out-patient for further injections. With regard to the question as to whether he should be detained overnight on the occasions of these later injections, this is decided by circumstances. If no reaction has occurred at the end of two hours, and if the soldier has not far to travel, he is allowed to return to his unit on the day of injection.

Subsequent observation depends on circumstances. Treatment having been continued until the Wassermann reaction is negative, the patient is at present required to attend for further observation monthly as long as he remains in this country, but he is available for inclusion in a draft for overseas at any time after the blood reaction has become negative, provided that he has also received the minimum course. In cases where it is probable that the advice will be followed, patients are advised to continue treatment with grey powder by the mouth.

The above representative examples of courses of treatment prescribed by different workers illustrate how far we have advanced from the original idea that one or two doses of ' 606 ' are sufficient to cure any case of syphilis. Many authors draw attention to the grave danger of syphilitic recurrences in the central nervous system which may result from insufficient treatment.

Syphilis of the Central Nervous System.

It is recognized as a general principle by those who have most experience in the treatment of syphilis of the central nervous system with the arsenical preparations, that, although a cautious start is always made, the patient should receive eventually very much more treatment than is considered sufficient for ordinary cases. Those who have followed the results of their treatment closely by periodical examination of the cerebro-spinal fluid show that it is extremely difficult to render this normal as regards Wassermann reaction, number of cells, and presence of globulin. In spite of this, it has been shown that by perseverance it is possible to render the cerebro-spinal fluid normal. The difficulty usually is that the patient will not persevere sufficiently long with the treatment.

While some workers confine themselves entirely to treatment through the blood stream, others supplement this with intrathecal injections of salvarsanized serum, mercurialized serum, or '914', claiming quicker results from this procedure. As representative of a treatment for which its author claims excellent results without intrathecal injections that of Dreyfus (141) may be mentioned. This worker varies his treatment according to the nature of the case, but on general principles believes in the efficacy of small doses repeated at frequent intervals.

The following is the general line which is adopted in the case of neurorecurrence or of syphilitic meningitis: On the first day a lumbar puncture is performed, and from the second to the eleventh day the patient is treated with mercury by inunctions or injections, the temperature being watched carefully. If at the end of this time the temperature is normal, '914' is commenced, with injections of 0·15, 0·3, and 0·6 grm. on the thirteenth, fourteenth, and sixteenth days. If any of these are followed by a rise of temperature to over 99°, the succeeding dose is reduced or the interval slightly lengthened. The '914' is continued in this manner until 1½ to 2 grm. have been administered, when '606' is commenced cautiously, with doses of 0·1, 0·2, 0·3 grm. on the succeeding four days, and the injections are continued at intervals of one or two days until 4 to 5 grm. have been given in the course.

A second course is administered after six to eight weeks, and a third after a similar interval from the end of the second course if the cerebro-spinal fluid has not yet become normal.

As to mercurial treatment, this is interrupted when the '914' is commenced and resumed after a dose of 0·6 grm. has been reached without disturbance. Naturally a close watch is kept for signs of intolerance, and doses reduced accordingly.

In cases of tertiary syphilis the course commences with injections of calomel, or of grey oil, on the third and fifth days, two days' rest having been allowed after the primary lumbar puncture. Injections of calomel, or of grey oil, are given weekly throughout the course, and the '606' is administered as follows:

Doses of 0·2, 0·3, 0·3, and 0·4 grm. are given on the seventh, ninth, fifteenth, and nineteenth days, and injections continued on the same principle for six to eight weeks until 4 to 5 grm. of '606' have been given. Dreyfus calculated that three to five such courses with suitable intervals are really necessary. The difficulty is that patients will not continue with the treatment, because long before this they have become symptomatically well.

In cases of tabes, the treatment commences with '606', and mercury is begun only after 1 to 2 grm. of the arsenical preparation have been administered. On the first, third, fifth, seventh, ninth, eleventh, and fourteenth days are given doses of 0·1, 0·2, 0·2, 0·2, 0·2, 0·3, and 0·3 grm. '606', continuing in this manner until 4 to 5 grm. have been given. It may happen that injections at first provoke crises, but the treatment is continued in spite of these. Great care is exercised over the administration of the mercury, as tabetics are often found to be intolerant of this remedy. The second course contains 3 to 4 grm. of '606', and Dreyfus calculates that four to six courses are necessary at intervals of two to three months. On such a treatment he has obtained results in the form of complete arrest of all symptoms which have lasted for three years. In 38 cases with severe lightning pains, 20 were very considerably improved, 14 were improved, and one showed no change. In 9 cases of perforating ulcer, bladder disturbance, &c., 3 were considerably improved, 4 improved, and 2 showed no change. In 18 cases of ataxia, 5 were considerably improved, 7 improved, 3 showed no change, and 3 became worse. In other forms of syphilis of the central nervous system the results from a symptomatic point of view were excellent, but the cerebro-spinal fluid was rendered normal only three times in 125 cases. Dreyfus attributes failures to render the fluid normal to lack of perseverance with the treatment on the part of the patient. He believes that, if the patient can only be induced to continue long enough, he can render the fluid normal in almost all cases of cerebro-spinal syphilis, and that most cases of tabes can be brought to a standstill.

Leredde claims that he has obtained normal, or nearly normal, cerebro-spinal fluid in many cases of tabes. His treatment would extend to the length of giving thirty to forty injections at suitable intervals on the plan already shown (p. 348). He also claims good results in cases of general paralysis from the administration of short courses of '914' at short intervals for a year or longer.

The difficulty of reaching the parenchyma of the central nervous system with antisyphilitic remedies administered through the blood-stream has induced numerous workers to test the effect of their introduction directly into the cerebro-spinal fluid, Wechselmann having probably been the first to demonstrate the safety of weak solutions of neosalvarsan injected into the spinal canal.

Swift and Ellis (142) introduced the method of injecting the patient's serum obtained within an hour of his receiving a full dose of '606'. As above mentioned, they showed that this serum had distinct antispirochaetal properties, especially when heated.

Swift's present technique is as follows (143) : Half an hour after an intravenous injection of '606' or '914' the patient is bled to an amount which is sufficient to yield 10 c.c. of serum. This is heated at 56° C. for forty-five minutes and injected intraspinally on the same day. Swift does not now find it necessary to dilute the serum as at first recommended, and as a general rule the patient can return to his home on the following day, having been in bed in the meantime. Generally speaking, injections should not be given more than once in three weeks. As to the treatment of syphilis of the central nervous system generally, Swift recommends that cases of syphilitic meningitis should commence with a short course of mercury, in order to avoid the risks of a Jarisch-Herxheimer reaction. If a gumma is suspected a vigorous course of potassium iodide should precede the more specific treatment. The line of treatment recommended is similar to that of Dreyfus mentioned above, with the addition that if after four to six months of intensive general treatment the reaction of the fluid shows no improvement, it may be well to resort to the intrathecal method. For tabes he recommends a commencement with small doses of '606', which are gradually increased and injected at intervals of a week, the course lasting six to eight weeks. If at the end of this time the Wassermann reaction of the fluid is much weaker, a course of mercury is tried, followed by another of '606', and so on in alternate courses, with periods of rest, until the fluid is brought to normal. In the numerous cases, however, in which this plan of treatment fails to affect the fluid, and especially in cases where the progress of the disease is acute, an early start with the combined intraspinal and intravenous treatment is recommended. Swift is very optimistic regarding the prognosis in cases treated on these lines. As to results, in thirty out of thirty-four cases of tabes, many of them advanced, which were treated by the combined intravenous and intraspinal methods, the Wassermann reaction became negative in 1 c.c. fluid, while in nineteen of the cases the fluid was negative even in 2 c.c. In general paresis, Swift, like other workers, has had indifferent results.

Gennerich (144), after trying the method of Swift and Ellis, now favours the direct introduction of '914' into the spinal canal. After finding that stronger concentrations were apt to cause untoward symptoms in the form of anaesthesia of the buttock, &c., with bladder and rectal disturbance, he finally recommended the injection of 4 to 6 c.c. of a 0·15 in 300 solution of '914', which was diluted still further with 12 to 15 c.c. of the fluid. The patient rested for two days after the injection, which was not repeated more often than once in two or three weeks. Schubert (145) recommended solution of the '914' in cerebro-spinal fluid. He dissolved 0·045 grm. of '914' in 3 c.c. of fluid, and of this took 0·1 to 0·2 c.c., which was placed in a funnel connected with the intraspinal canula. Before addition of the '914' solution, some of the cerebro-spinal fluid was allowed to run into the funnel by lowering it.

The intraspinal injection of serum to which '606' or '914' has been directly added, as recommended by Ogilvie, has been extensively used in America,

and is the method now preferred by Fordyce (146). To 8 or 10 c.c. of the patient's serum, which must be completely free from red cells, is added 0·05 to 0·5 mg. of ' 606 ', and the solution is incubated at 37° C. for 30 minutes. The initial dose for cases of tabes is 0·05 to 0·1 mg., and this is gradually increased to 0·2 to 0·3 mg., according to the patient's toleration. Swift recommends that the serum of a salvarsanized patient should be used for this purpose. The blood drawn off an hour after injection should be allowed to remain in contact with the clot overnight, and after the addition of the arsenical preparation it should be heated to 56° C., as recommended for serum which has been salvarsanized *in vivo.*

Following the recommendation of Byrnes, various workers have tried the injection of mercurialized serum. As practised by Wolfsohn (147), who has slightly modified the original technique, the procedure is as follows :

1. The patient receives full doses of mercury by inunctions for a week.

2. An amount of blood which is sufficient to yield 18 to 20 c.c. of serum (about 40 c.c. of blood) is drawn off, centrifugalized, placed in a refrigerator for 18 to 24 hours, again centrifugalized for 15 to 20 minutes, and the serum pipetted off.

3. To this serum is added 1 c.c. of a solution containing $\frac{1}{50}$ of a grain of mercuric chloride in distilled water.

4. The prepared serum, which should be perfectly clear, is heated at 56° C. for half an hour.

5. Spinal fluid is removed by lumbar puncture until its pressure reads about 30 mm., when the prepared serum is slowly administered by gravity at body temperature. The patient is put to bed with the foot of the bed elevated for four hours.

On an average, five injections are administered at intervals of one to five weeks. Wolfsohn concludes with regard to the method, that it is very efficient in syphilis of the central nervous system, especially in tabes with severe lightning pains. Also, it has the advantage of stability, and is perfectly safe provided that care is taken not to introduce haemoglobin with the serum.

A study of the case-records advanced by the different writers in favour of intrathecal injections leaves one with the impression that, as with the ordinary methods of administration, the treatment must be prolonged to effect good results. In a few cases in which the writer has attempted, after rather prolonged systemic treatment, to improve the state of the cerebro-spinal fluid still further by intrathecal injections, no great effect was produced. It is possible that the lumbar puncture itself may sometimes be a factor in the rapidity of the symptomatic improvement which has been noted in many cases treated by the intrathecal method. In a case of tabes which was under the care of the writer, where no antisyphilitic treatment had been administered previously, simple lumbar puncture carried out for diagnostic purposes resulted in complete recovery from paralysis of the bladder within a few hours. In those cases which are treated with combined intraspinal and intravenous injections the latter may

easily be a considerable factor in the improvement, since there is no doubt that the long-continued administration of ' 606 ' or '914' through the blood-stream will effect much in reducing the number of lymphocytes and the strength of the Wassermann reaction in the fluid.

It will be seen from the above that, although much success has been obtained in the treatment of syphilis of the central nervous system and in tabes, this has not been by the administration of one or two full doses of ' 606 ' and abandonment of the treatment if the patient appeared to be worse immediately afterwards, but by the long-continued administration of small doses fairly frequently repeated and in courses of 4 to 5 grm. each. Practically all who have experience in the treatment of syphilis of the central nervous system agree that unless the patient is willing to persevere until he has received a substantial amount of the arsenical remedy, it is better to withhold the latter. This applies especially to cases of tabes.

As to the safety of arsenical treatment in cases of the nature mentioned, the writer is convinced that, when administered on the lines suggested above, ' 606 ' or ' 914 ' can be injected without fear. At Rochester Row cases of comparatively advanced tabes have received as many as twenty-eight intravenous injections of ' 606 ' and twenty-one intramuscular injections of ' 914 ', with benefit.

The greatest effect is almost always produced on the cells, which are very rapidly reduced to normal, or nearly normal limits. For instance, in one case of pseudo-tabes, three months' treatment reduced the cells from 363 per c.mm. to 9 per c.mm., and two months later they were 2 per c.mm. In another, of tabes with well-developed ataxia, 720 cells per c.mm. were reduced to 4 per c.mm. in three months. The Wassermann reaction is more difficult to influence, but in the first of the above cases three months' treatment reduced a strongly positive reaction in the equivalent of 0·2 c.c. fluid to a doubtful reaction in 1 c.c.   In these, as in other cases, the treatment was by alternate intravenous injections of ' 606 ' (0·3 grm.) and intramuscular of ' 914 ' (0·3 grm.), one of each being given every week, commencing one week after an initial dose of 0·2 grm.   Mercury and potassium iodide are also administered in these cases, the iodide sometimes concurrently with the other remedies, sometimes in the intervals of rest. It is a frequent observation that when iodide is given during the interval the patient seems to make more rapid progress than he has shown during the course of injections.

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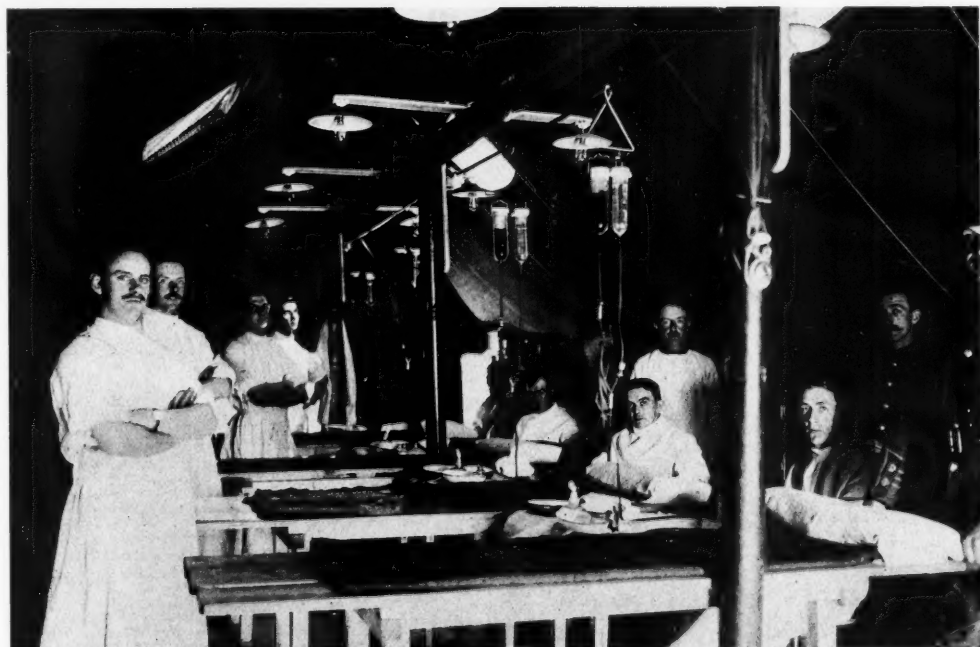
WRITER'S ARRANGEMENT FOR THE ADMINISTRATION OF '606' ON A LARGE SCALE IN A B.E.F. HOSPITAL.

A.   For six injections at one time in a hut.   One set of apparatus missing.

B.   The same (earlier date) for four injections at one time in a large hospital marquee.   On left, one orderly to each table.   On right, standing, supervising medical officer (in white), responsible also for the mixing of the solutions.   Next him, standing, chief clerk, responsible, *inter alia*, for making out the daily programme of injections from the treatment cards.   Seated, medical officers responsible for the actual injections ; number of medical officers subsequently reduced to one per two or three tables.

A NOTE ON PURPURA IN MENINGOCOCCAL INFECTIONS

By T. R. ELLIOTT and H. W. KAYE

With Plate 35

MOST of the reports that have been published since the beginning of the War on military cases of cerebro-spinal fever lay but little stress on the appearance of a rash. Bourke, Abrahams, and Rowland (1) describe the features of 161 cases that were observed at one isolation hospital in France, but they do not refer to the rash among the points discussed in their paper.

H. R. Brown (2), however, noted that a petechial rash was present in 30 per cent. of the twenty-seven cases that he had seen at another hospital in the same area; and McNee (3) states that a rash could be observed in at least 20 per cent. of those which he had seen at the beginning of the third day of illness. Flack's (4) report on sixty-one cases from the London district gives the rash as a minor feature that was present in about 13 per cent.

Brown analysed the character of the rashes that he had observed. The common form was a petechial rash, resembling flea-bites, which faded in four days, and the presence of which bore no special relationship to the severity of the case. He observed one example of large purpuric spots distributed all over the trunk and thighs, which also faded on the fourth day after their appearance. He distinguished this true rash from the purpuric mottling of the extremities which may develop when death is imminent, and is common to fatal cases of sepsis from various causes.

Several medical officers have met with fulminating and rapidly fatal cases of fever associated with a purpuric rash, which were proved to be caused by a meningococcal septicaemia; and this experience is so well known that the suspicion of a meningococcal infection is always raised now in the minds of clinicians when they have to deal with a case of fever that exhibits a petechial or purpuric rash, even though no symptoms of meningeal inflammation can at first be detected. We are not aware of any evidence which shows clearly whether these spots on the skin are to be regarded as a toxic rash or as a focal eruption caused by the local development of colonies of meningococci that had been distributed in a septicaemia. Blood cultures have not been systematically made by workers from cases of cerebro-spinal meningitis with a rash.

The first case that we describe is a most clearly cut example of this fulminating type.

Case I. Meningococcal septicaemia: death in twenty-four hours after onset.

Pte. A. E. W. marched 11 miles with his battalion on April 4, 1916, and did not feel ill enough to report sick till midday on April 5. When seen at a Casualty Clearing Station a few hours later he was extremely ill. Temperature 101·6°; pulse 144, being small and irregular; respirations 44 per minute. The tongue was brown and furred.

On examining his legs, in which he complained of great pain, a most unusual and striking appearance was seen. Bluish-black blotches, of irregular shape and of various sizes, but many of them as large as a penny, were found scattered all over the lower limbs and buttocks, while a few were evident on the arms. The ankles and feet were exceedingly tender: knee-jerks were brisk and equal: plantar reflexes were flexor in type: Kernig's sign was not obtained, nor was there any stiffness or pain in the neck muscles. He complained of slight headache, but apart from this no symptoms or sign of meningeal irritation could be elicited. The heart was normal in size and position, and the only abnormal physical signs in the lungs were those suggesting early pneumonia or a thin layer of fluid with some collapse of the left lower lobe.

His condition showed no material change during the remaining few hours of his life, and he died at 12.15 a.m. on April 5, *well within twenty-four hours of the time at which he first felt ill enough to report sick.*

An autopsy on the day of death showed as follows:

'The lower limbs and buttocks present numerous pale blue-black blotches, which are of irregular shape and vary in size from a pin's head to 3 cm. in diameter. They are present on both surfaces of the lower limbs, being more numerous and larger towards the lower part and especially upon the feet. A few are scattered on the arms and forearms, where they are for the most part smaller; there are none upon the hands, trunk, face, or neck. On section they are seen to consist of haemorrhages into the deeper layers of the skin, and not to be raised above the general surface. No bacteriological or microscopic examination of these patches were made.

'*Brain and cord.* The cortical veins are distended with dark fluid blood. This congestion is especially evident all over the vertex and gradually diminishes over the lateral aspects of the cerebrum till it disappears at the margin of the cisterna magna. There is no flattening of the cerebral convolutions. No excess of fluid in the ventricles; no haemorrhages; no fibrinous deposit or "stickiness" to be found anywhere. The cord appears perfectly normal, both externally and upon section at various levels. In short, with the exception of the above vascular condition, the brain and cord are quite devoid of any abnormal appearances to the naked eye.

'The left pleural cavity contains 10 to 15 oz. of brownish-yellow clear fluid, and the same quantity of blood-stained fluid is found in the right pleural cavity. The parietal pleurae are universally injected, and the visceral pleurae show a few tiny scattered haemorrhages. Both lungs are firm to the touch, and the cut surface exudes much frothy fluid on squeezing: sections float in water.

'The spleen is large, soft, and friable. The kidneys are unusually large, pale, and firm: on section, their substance bulges and curls up over the cut edge of the capsule, and that of the cortex is covered with glistening, slightly raised points and streaks. The urine was not examined. Similar congestion and enlargement was observed in the liver. No abnormal condition was noticed in any of the other organs.'

Captain A. W. M. Ellis, C.A.M.S. (Mobile Laboratory), had taken samples of the blood and cerebro-spinal fluid at 10 p.m. on April 5, that is four hours

before death, and he reported as follows: ' The blood was inoculated into plain broth, which showed a fairly profuse growth of a Gram-negative diplococcus in eighteen hours. Prolonged search of film preparations from the blood failed to show any micro-organism. A blood count was not made, but the appearance of the films suggested the existence of a leucocytosis, and a differential count of 500 cells showed a considerable increase of large mononuclear cells.

' The cerebro-spinal fluid from lumbar puncture was absolutely clear and limpid, giving neither sediment on centrifugalization nor clot on standing. Cell count 12 per c.mm., of which 11 were polymorphonuclear leucocytes. The fluid was centrifuged and then poured off, after which the tube was inverted and allowed to drain. The small amount of fluid remaining adherent to the walls of the tube was then picked up with a fine capillary pipette and smeared on a glass slide. This smear when stained showed a few cells, chiefly poly-morphonuclear leucocytes, and large numbers of diplococci, which were morphologically meningococci. They were practically all extra-cellular, and were so numerous that fifty to ninety pairs were frequently seen in one microscopic field.

' Culture and inoculation showed the organisms isolated from the blood and from the cerebro-spinal fluid to be identical, and to be a true " Type 1 " meningococcus (5).'

The case just described accords with the general experience that extensive and early purpura in a case of meningococcal infection (cp. McNee (3)) usually indicates a fatal prognosis.

The second case that we quote is anomalous, because the development of the purpura in it seems to have been influenced by the complication of trench feet, which resulted from exposure to severe cold in the trenches during the period of prostration at the onset of the illness.

Case II.   Trench feet associated with necrotic purpura from cerebro-spinal meningitis.

Pte. H. ——, —— Regiment, aged 23. Eight months' service at front in France, during which time he had never gone sick, and had never suffered trouble with his feet while in the trenches during the winter.

About January 31, 1917, he suddenly fell ill with headache and shivering, but no vomiting, and with severe pain in both legs. The weather was severe, an intense frost having commenced on January 23. The patient had been in the trenches for six days, wearing rubber thigh waders which reached up to the gluteal folds; but his legs had been dry and warm throughout and there was nothing the matter with them immediately before the illness, although he had been wading through icy water. He had not been suffering from any cold in the head.

The patient lay down with his waders on in a reserve trench and did not at once report sick. About thirty hours later he was seen by the medical officer. The waders were then removed and his feet were noticed to be cold, but pre-sumably no striking changes were visible because the patient was subsequently passed through a field ambulance with the diagnosis of ' Pyrexia of unknown origin '.

February 2–3. The night was passed in a Central Clearing Station, where he talked continually in semi-delirious sleep and was ignorant of the state of

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his legs. T. subnormal; P. 120; R. 20. Purpura and frost-bite were now obvious on this the third day of the illness, and the case was sent down with a special note calling attention to its unusual features.

February 3. Transferred to Base Hospital, where he came under the care of Captain H. Wilks, R.A.M.C., who recognized the probability of meningococcal infection and drew our attention to the case.

February 4. Patient was perfectly conscious but complaining of headache, and he had passed water in the bed during the night. Slight stiffness of neck: abdominal reflexes lost: the thighs were too tender and painful for Kernig's sign to be tested.

The legs showed the extraordinary appearance which is depicted in the drawing made on the same day by Sergt. A. K. Maxwell, R.A.M.C. (Plate 35). From the ankles downwards the feet were grey, cold, anaesthetic, and powerless; the circulation in them had ceased. Upon the legs and thighs above this dead area was a purpuric rash of irregular distribution with red edges and central areas of greyish purple tint which looked as though they would soon become necrotic.

There was no rash elsewhere on the body except for three tiny purpuric spots on the left wrist. The finger-tips were cold and numb. There was a small patch of herpes on the upper lip.

It was evident that the patient was suffering from trench feet with serious circulatory failure in them, but the feet were neither blistered nor septic, so that it did not appear likely that from them had been derived the toxic substances which had led to the purpura higher up the limbs.

February 5. Captain H. Henry reported that blood culture was negative, but that lumbar puncture had yielded a cloudy fluid containing intracellular diplococci in the film and giving definite meningococci on culture. The patient was at once transferred to an isolation hospital, before blisters could be applied to the edge of the purpuric patch as a test for the presence of meningococci in these foci.

February 6. Neck not stiff: abdominal reflexes still absent. Lumbar puncture yielded 50 c.c. of cloudy fluid containing cells with 90 per cent. of polymorphs but no organisms.

February 8. The finger-tips were now cold and discoloured. The necrotic areas on the thighs and legs had become almost coal black at their periphery.

February 25. The patient had recovered completely from his meningeal symptoms and looked very well, despite the severe sepsis in his lower limbs. Captain Walmisley, under whose care he had been since February 6, regarded the clinical features of cerebro-spinal meningitis as having been of the mildest character throughout. No special serum had been used intraspinally, and anti-tetanic serum had never been injected for the trench feet.

The pulp of the finger-tips in both hands was now shrivelled and blue, resembling the late results of a mild attack of Raynaud's gangrene. Both the feet were dead and gangrenous up to a line of demarcation about a couple of inches above the malleoli.

The legs and thighs showed enormous areas of ulceration from which the necrosed skin had sloughed away and laid bare the subcutaneous tissues. These areas were now covered with healthy granulations, and the skin at their edges was growing vigorously.

March 5. The gangrenous feet were both removed by amputation. The patient recovered well from the operation, and continued to improve, though the ulcerated areas on the thighs were slow in healing (March 10).

Necrotic purpura of the character and distribution seen in Case II has never been observed to our knowledge in ordinary frost-bite of the legs, so that its presence here must be ascribed to the complicating factor of meningococcal

infection.   But purpura in cerebro-spinal meningitis is not restricted in its distribution to the lower extremities ; and it is most rare for it to be followed by necrosis, partly perhaps for the reason that, when severe, it is usually associated with so overwhelming an infection that death ensues before the local necrotic changes can make themselves manifest.

The possibility of necrosis following upon purpura in a very severe form of infection is illustrated by a case quoted by Dr. Robb of Belfast (6), February 6, 1915, in which there was a plentiful petechial eruption together with large patches of haemorrhagic purpura on feet, knees, hands, ears, and also with sub-conjunctival haemorrhages.   At this time the patient was unconscious and he seemed most dangerously ill, though he slowly recovered under serum treatment. During the recovery several patches of purpuric skin became necrosed and sloughed away.

In Dr. Robb's case the rash was widely distributed and the illness of the most alarming gravity.   But Case II did not conform to this type, for the rash was practically confined to the legs and the meningococcal infection was other-wise so trifling in its features that the diagnosis might easily have been missed. The probable explanation is that the infection normally would not have been accompanied by any rash at all, but that the defenceless exposure to cold during general prostration at its onset led not only to the development of trench feet, but also to an outbreak of purpura which was localized in the chilled areas of skin under the waders.   Since the fronts of the thighs as well as the nates were affected, it is obvious that the localization was not of that of pressure surfaces. It should be noted that the hands were slightly frost-bitten ; and that there was a little purpura on the wrist.

How cold acted in determining this outcrop of purpura remains a matter for conjecture, because there are not enough facts known to give a true analysis of the pathological process.   Blood infection was not proved to exist, and Captain Henry was unable to blister the purpuric areas in search for meningococci.   But inasmuch as the meningococcus is an organism of the most delicate sensitiveness to cold, it seems unlikely that the great purpuric patches should have been the index of local colonies that had found their chance to establish themselves under the skin because these areas were chilled.   The history from the Central Clearing Station tells that the purpura appeared simultaneously with the trench feet, and very soon after the waders had been removed ; so that we can hardly take the explanation that the legs were first chilled and devitalized, and that at a later period, when the circulation improved, meningococci commenced to grow in the subcutaneous tissues which were now warmed but had lost their original powers of resistance.   It therefore appears legitimate to assume that the purpuric rash was not focal but toxic.

The influence of cold or imperfect circulation in determining the distribution of rashes has often attracted the thought of clinicians, but generalizations have not been made on this subject, because each infection seems to have its own laws of reaction in this respect.   For example, the toxic prodromal rash of